HUMAN GENETIC ENGINEERING

HEARINGS

BEFORE THE

SUBCOMMITTEE ON
INVESTIGATIONS AND OVERSIGHT

OF THE

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SCIENCE AND TECHNOLOGY
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HUMAN GENETIC ENGINEERING

TUESDAY, NOVEMBER 16, 1982

House of Representatives,
Committee on Science and Technology,
Subcommittee on Investigations and Oversight,
Washington, D.C.

The subcommittee met, pursuant to call, at 9:30 a.m., in room 1650, Longworth House Office Building, Hon. Albert Gore, Jr. (chairman of the subcommittee) presiding.

Mr. Gore. The subcommittee will come to order.

I would like to welcome all of our guests and our witnesses today. We have been looking forward to this series of hearings. I want to say at the outset that the staff of the subcommittee has worked awfully hard for about 6 months in preparing this inquiry. For the next 3 days we are going to investigate the questions posed by human genetic engineering very thoroughly.

I want to thank all of you—I see many people in the audience here today who have guided us and helped us in trying to frame the questions, and I want to thank you for that. I will do so to individuals as the hearings move forward.

As I said, this is the first of 3 days of hearings. We are going to do this fairly methodically. We are going to start with an overview of the questions with the Executive Director of the President's Commission, Alex Capron. Then we are going to look at the basics of the science itself. And then we are going to look at the applications to human beings. Then we will move on to religious and ethical, moral concerns, tomorrow and the third day.

In the mid-19th century, a scientist and monk named Gregor Mendel conducted a series of experiments on ordinary garden peas. In his experiments Mendel observed that desirable characteristics in peas could be encouraged through cross-breeding and then passed on to later generations of plants. From these experiments Mendel formulated his theory of genetics, and from this simple beginning the modern-day science of genetics has evolved.

In the years since Mendel conducted his experiments, tremendous advances have occurred in genetic science. The discovery of the DNA double helix in 1953 by Drs. Watson and Crick ushered in a revolution in science's comprehension of the nature, structure, and function of genes. Today science possesses an astounding comprehension of the genetic basis of life and its knowledge is increasing in exponential proportions.

Like Mendel, modern geneticists have sought ways to control genetic processes. With the discovery of restriction enzymes, scientists in the 1970's developed the ability through recombinant DNA techniques to identify, splice, and transfer genes in and between organisms. As a result of these developments, biotechnological achievements in industry, agriculture, and the health sciences have been phenomenal. New discoveries seem to be announced almost monthly.

As science has increased its gene-splicing abilities in other areas, it has simultaneously progressed toward the ultimate biotechnology: human genetic engineering. Human genetic engineering was once thought to be impossible, the product of science fiction writers' vivid imaginations. Like so many other accomplishments in science and technology, however, human genetic engineering has moved from the realm of impossibility to certainty. The real question today thus is not whether human engineering will become a reality but, rather, when it will be so and for what purposes it will be used.

This subcommittee has held numerous hearings on many aspects of genetic technology. We have examined the industrial and agricultural uses of recombinant DNA techniques and have focused on the issue of genetic screening in the workplace. In each of those areas, we discovered that the technology had developed far more rapidly than had been anticipated. Today, with our review of human genetic engineering, the subcommittee takes the next and most important step in its consideration of issues in genetic technology. And again, it seems science has far outpaced expectations and predictions.

Recent developments in genetic research portend the imminence of human genetic engineering. As we will hear this morning, gene transplants have been successfully performed on laboratory animals, and the expectation is that these achievements will pave the way for similar transplants in humans. Moreover, one scientist actually attempted gene transplants on humans 2 years ago, and we will hear from him about that during the course of this hearing. The recent achievements in the labs will surely encourage new thoughts of human experimentation.

Indeed, our final witness to today's panel will have some provocative statements about that subject.

The potential development of the power to alter our genetic constitution gives us cause for both hope and concern. As we will hear today, a number of diseases are known to be caused by gene defects, and it is said that these diseases could likely be cured through human gene therapy. However, these miraculous developments are not taking place in a vacuum. Other potential uses of this new science, such as the manipulation of physical traits and mental capacities, raise enormous questions of ethics, religion, and morality that our society must be prepared to confront. In many respects, we will be grappling with one of the most fundamental questions of all: What does it mean to be human?

The purpose of this hearing is to examine the questions raised by human genetic engineering, the composite of which I call "genethics." During the next 3 days, the subcommittee will hear testimony from scientists, religious leaders, ethicists, philosophers, sociologists, and others involved in the genetic engineering debate. While we do not expect answers to all our questions, we do hope to begin to identify the issues involved.

Today's discussion will focus principally on the scientific state of the art in human genetic engineering; what is possible now, what will be possible in the near future, and what may be impossible.

One panel will focus on basic recombinant DNA techniques. The other will discuss the specific human applications of those techniques. Together they will help us separate science fact from science fiction.

Tomorrow we will examine the religious and ethical concerns associated with human genetic engineering; are scientists really "playing God?" Are human genetic experiments morally and ethically justifiable? Where do we draw the line on treatments?

On the third day of our hearing, we will consider the future course of human genetic research from a societal perspective and hear proposals for mechanisms to more closely oversee its progress. As is so often the case with scientific achievement, the technology here will surpass the ability of our existing social, ethical, and political institutions to deal with it unless we have adequately considered its ramifacations beforehand. Already signs of strain are evident. New mechanisms may have to be constructed to handle the problems the technology will bring.

To begin our discussion today, we will hear from Prof. Alex Capron, the Executive Director of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. The President's Commission has spent the last 2 years studying the social and ethical issues inherent in human genetic engineering. Professor Capron is here to present the Commission's report and help us begin our examination.

Professor Capron, if you would come to the witness table, we are honored to have you as our lead-off witness, to give us an overview of this important set of developments. Every time I have an opportunity to receive testimony from you and to ask you questions, I compliment your work again. But let me say that even though that may be getting old for you, I think it is an important part of any hearing record in which you participate.

The record of this Commission is one of the remarkable success stories of the efforts of a democracy to look closely at ethical and bioethical questions. And I think our country can take a great deal of pride in the work that has been done under your leadership at the Commission.

Without objection, the full text of your testimony will be put into the record. I will invite you to present it at this time.

STATEMENT OF PROF. ALEXANDER MORGAN CAPRON, EXECUTIVE DIRECTOR, PRESIDENT'S COMMISSION FOR THE STUDY OF ETHICAL PROBLEMS IN MEDICINE AND BIOMEDICAL AND BEHAVIORAL RESEARCH

Mr. CAPRON. Thank you very much, Mr. Chairman, for those kind words.

Morris B. Abram, the Chairman of the President's Commission, regrets that he is unable to be here this morning and has asked that I provide you with an overview of the ethical and social issues raised by the human uses of genetic engineering.

As you mentioned, this has been one of the topics that the Commission has undertaken, an additional topic to those in our original congressional mandate. Last Friday, at the Commission's meeting, agreement was reached on a draft report, and it is my pleasure to have it here to present to you today.

Mr. GORE. If you could give us the report, without objection, include it in full at this point in the record, and we will provide the Commission with ample opportunity to perform the last-minute corrections that you referred to before the hearing record is published.

[The report mentioned above follows:]

Splicing Life

A Report on the Social and Ethical Issues of Genetic Engineering with Human Beings

November 1982

President's Commission for the Study of
Ethical Problems in Medicine and
Biomedical and Behavioral Research

President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research

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SUMMARY OF CONCLUSIONS AND RECOMMENDATIONS

This Report addresses some of the major ethical and social implications of biologists' newly gained ability to manipulate--indeed, literally to splice together--the material that is responsible for the different forms of life on earth. The Commission began this study because of an urgent concern expressed to the President that no governmental body was "exercising adequate oversight or control, nor addressing the fundamental ethical questions" of these techniques, known collectively as "genetic engineering," particularly as they might be applied directly to human beings.[1]

When it first examined the question of governmental activity in this area, in the summer of 1980, the Commission found that this concern was well founded. Not only was no single agency charged with exploring this field but a number of the agencies that would have been expected to be involved with aspects of the subject were unprepared to deal with it, and the Federal interagency body set up to coordinate the field was not offering any continuing leadership. Two years later, possibly because of the Commission's attention, it appears the Federal agencies are more aware of, and are beginning to deal with, questions arising from genetic engineering, although their efforts primarily address the agricultural, industrial, and pharmaceutical uses of gene splicing rather than its diagnostic and therapeutic uses in human beings.[2]

The Commission did not restrict its examination of the subject to the responses of Federal agencies, however, because it perceived more important issues of substance behind the expressed concern about the lack of Federal oversight. The Commission chose, therefore, to address these underlying issues, although certainly not to dispose of them. On many points, the Commission sees its contribution as stimulating thoughtful, long-term discussion rather than truncating such thinking with premature conclusions.

This study, undertaken within the time limitations imposed by the Commission's authorizing statute, is seen by the Commission as a first step in what ought to be a continuing public examination of the emerging questions posed by developments and prospects in the human applications of molecular genetics. First the report attempts to clarify concerns about genetic engineering and to provide technical background intended to increase public understanding of the capabilities and potential of the technique. Next, it evaluates the issues of concern in ways meaningful for public policy and analyses the need for an oversight mechanism.

To summarize, in this initial study the Commission finds that:

(1) Although public concern about gene splicing arose in the context of laboratory research with microorganisms, it seemed to reflect a deeper anxiety that work in this field might remake human beings, like Dr. Frankenstein's monster. These concerns seem to the Commission to be exaggerated. It is true that the genetic engineering techniques are not only a powerful new tool for manipulating nature--including means of curing human illness--but also a challenge to some deeply held feelings about the meaning of being human and of family lineage. But as a product of human investigation and ingenuity, the new knowledge is a celebration of human creativity, and the new powers are a reminder of human obligations to act responsibly.

(2) Genetic engineering techniques are advancing very rapidly. Two breakthroughs in animal experiments during 1981 and 1982, for example, bring human applications of gene splicing closer: in one, genetic defects have been corrected in fruit flies; in another, artificially inserted genes have functioned in succeeding generations of mammals.

(3) Genetic engineering techniques are already demonstrating their great potential value for human well-being. The aid that these new developments may provide in the relief of human suffering is an ethical reason for encouraging them.

- Although the initial benefits to human health involve pharmaceutical applications of the techniques, direct diagnostic and therapeutic uses are being tested and some are already in use. Those called upon to review such research with human subjects, such as local Institutional Review Boards, should be assured of access to expert advice on any special risks or uncertainties presented by particular types of genetic engineering.
- Use of the new techniques in genetic screening will magnify the ethical considerations already seen in that field because they will allow a larger number of diseases to be detected before clinical symptoms are manifest and because the ability to identify a much wider range of genetic traits and conditions will greatly enlarge the demand for, and even the objectives of, prenatal diagnosis.

(4) Many human uses of genetic engineering resemble accepted forms of diagnosis and treatment employing other techniques. The novelty of gene splicing ought not to erect any automatic impediment to its use but rather should provoke thoughtful analysis.

- Especially close scrutiny is appropriate for any procedures that would create inheritable genetic changes; such interventions differ from prior medical interventions that have not altered the genes passed on to patients' offspring.
- Interventions aimed at enhancing "normal" people, as opposed to remedying recognized genetic defects, are also problematic, especially since distinguishing "medical treatment" from "nonmedical enhancement" is a very subjective matter; the difficulty of drawing a line suggests the danger of drifting toward attempts to "perfect" human beings once the door of "enhancement" is opened.

(5) Questions about the propriety of gene splicing are sometimes phrased as objections to people "playing God." The Commission is not persuaded that the scientific procedures in question are inherently inappropriate for human use. It does believe, nevertheless, that objections of this sort, which are strongly felt by many people, deserve serious attention and that they serve as a valuable reminder that great powers imply great responsibility. If beneficial rather than catastrophic consequences are to flow from the use of "God-like" powers, an unusual degree of care will be needed with novel applications.

(6) The generally very reassuring results of laboratory safety measures have led to a relaxation of the rules governing gene splicing research that were established when there was widespread concern about the potential risks of the research. The lack of definitive proof of danger or its absence has meant that the outcome--whether to restrict certain research--has turned on which side is assigned the burden of proving

its case. Today those regulating gene splicing research operate from the assumption that most such research is safe, when conducted according to normal scientific standards; those opposing that position face the task of proving otherwise.

- The safety issue will arise in a wider context as gene splicing is employed in manufacturing, in agriculture and other activities in the general environment, and in medical treatment. As a matter of prudence, such initial steps should be accompanied by renewed attention to the issue of risk (and by continued research on that subject).
- Efforts to educate the newly exposed population to the appropriate precautions, whenever required, and serious efforts to monitor the new settings (since greater exposure increases the opportunity to detect low-frequency events) should be encouraged. In general, the questions of safety concerning gene splicing should not be viewed any differently than comparable issues presented by other scientific and commercial activities.

(7) The Recombinant DNA Advisory Committee (RAC) at the National Institutes of Health has been the lead Federal agency in genetic engineering. Its guidelines for laboratory research have evolved over the past seven years in response to changes in scientific attitudes and knowledge about the risks of different types of genetic engineering. The time has now come to broaden the area under scrutiny to include issues raised by the intended uses of the technique rather than solely

the unintended exposure from laboratory experiments.

- It would also be desirable for this "next generation" RAC to be independent of Federal funding bodies such as NIH, which is the major Federal sponsor of gene splicing research, to avoid any real or perceived conflict of interest.

(8) The process of scrutiny should involve a range of participants with different backgrounds—not only the Congress and Executive Branch agencies but also scientific and academic associations, industrial and commercial groups, ethicists, lawyers, religious and educational leaders, and members of the general public.

- Several formats deserve consideration, including initial reliance on voluntary bodies of mixed public-private membership. Alternatively, the task could be assigned to this Commission's successor, as one among a variety of issues in medicine and research before such a body, or to a commission concerned solely with gene splicing.
- Whatever format is chosen, the group should be broadly based and not dominated by geneticists or other scientists, although it should be able to turn to experts to advise it on the laboratory, agricultural, environmental, industrial, pharmaceutical, and human uses of the technology as well as on international scientific and legal controls. Means for direct liaison with the government departments and agencies involved in this field will also be needed.

(9) The need for an appropriate oversight body is based upon the profound nature of the implications of gene splicing as applied to

human beings, not upon any immediate threat of harm. Just as it is necessary to run risks and to accept change in order to reap the benefits of scientific progress, it is also desirable that society have means of providing its "informed consent," based upon reasonable assurances that risks have been minimized and that changes will occur within an

FOOTNOTES

1. See Appendix B, at pp. ___ - ___ *infra*.
2. See Appendix C, at pp. ___ - ___ *infra*.

CHAPTER 1: CLARIFYING THE ISSUES

Human beings continually pursue greater knowledge about themselves and their world. Science provides a powerful key in that quest, unlocking many mysteries. But even as science answers questions, it generates many new ones; new knowledge creates new challenges. The recently acquired capability to manipulate the genetic material of all living things is an important--even revolutionary--advance in the trajectory of human knowledge. But, like revolutionary insights of the past that enriched understanding, it also unsettles notions that once seemed fixed and comfortable. This Report attempts to contribute to the public discussion of the social and ethical implications of genetic engineering by clarifying some of the issues raised by the new technology and initiating an examination of possible procedural mechanisms for responding to them.

The Commission undertook this study in response to a request addressed to the President on June 20, 1980, by the General Secretaries of the National Council of Churches, the Synagogue Council of America, and the United States Catholic Conference. In the wake of the Supreme Court decision that allowed the patenting of new forms of life, the religious organizations warned that

> We are rapidly moving into a new era of fundamental danger triggered by the rapid growth of genetic engineering. Albeit, there may be opportunity for doing good; the very term suggests the danger.[1]

Describing the questions as "moral, ethical, and religious, [dealing] with the fundamental nature of human life and the dignity and worth of the individual human being," the three religious representatives called upon President Carter to remedy the lack of "adequate oversight or control" among governmental bodies by providing "a way for representatives of a broad spectrum of our society to consider these matters and advise the government on its necessary role." In response to a request from the President's Science Advisor, the Commission decided in September 1980 to study the ethical and social implications of this new area of biotechnology as it applies to human beings.

A. The Meaning of the Term "Genetic Engineering"

1. Changes in the Genetic Landscape. For at least 10,000 years--since long before the principles of classical genetics[2] had been scientifically established—human beings have brought about deliberate genetic changes in plants and animals through traditional reproductive methods. Many of the domestic animals, crops, and ornamental plants in existence today are human creations, achieved through selective breeding aimed at enhancing desired characteristics. In a broad sense, such genetic manipulation by breeding for a desired outcome might be considered genetic "engineering."

In addition to these intended changes, many alterations have occurred inadvertently through other practices, including the ordinary practice of medicine. Many people with genetic disorders who in the past would have died without any natural-born children now live into adulthood, passing on genes for the disorder. The use of exogenous insulin to treat diabetes and the prescription of eyeglasses for myopia are two examples of interventions that increase the prevalence in the population of certain genes that can have deleterious effects for individuals. Medical screening for genetic disorders and carrier status, when followed by decisions by the individuals screened to alter reproductive behavior, also affects the occurrence of genes in the population.[3] These changes have been a by-product of medical and technological interventions aimed at individuals, not at the general population.

2. Manipulating Genes. In 1965 the term "genetic engineering" was coined for what has come to be a wide range of techniques by which scientists can add genetically determined characteristics to cells that would not otherwise have possessed them.[4] Compared with traditional means of altering the gene pool, the ability to alter genetic material directly offers specificity and, in the case of changes in germ cells, speed.

The rapidity with which this field has developed is startling. Scientists' understanding of the structure of deoxyribonucleic acid (DNA), which is common to almost all living cells, and their discovery of its remarkable capacity for encoding and passing on genetic characteristics are post-1953 developments. In the early 1970s, scientists learned how to isolate specific DNA sequences from one species and attach this genetic material--"recombinant DNA"--to a different species. Rapid progress has also been made with cell fusion, another means of genetic engineering that permits the contents of two cells from different organisms to be merged in such a way that the hybrid cell continues to function and reproduce.

The layperson's term "gene splicing" describes the technology well, for like a seaman putting two pieces of rope together, a scientist using the recombinant DNA method can chemically "snip" a DNA chain at a predetermined place and attach another piece of DNA at that site. In cell fusion, it is two entire cells that are "spliced" together.

Chapter Two provides a fuller discussion of gene splicing and its applications.

The term genetic engineering has sometimes been used to refer to several other new technologies such as in vitro fertilization[5] and cloning[6] of an organism. These techniques do not necessarily involve genetic manipulation, although they might be used in conjunction with such manipulation in particular situations. They are regarded here as examples of reproductive (rather than genetic) technologies and thus are outside the scope of this Report.

B. Concerns About Genetic Engineering

Genes are perhaps the most tangible correlates of who a person is as an individual and as a member of a family, race, and species. They are people's fixed legacy to their descendants. Genetic information can alter an individual's most personal decisions about reproduction. It is not surprising, therefore, that genetics is peculiarly prone to controversy.

1. Scientific Self-Regulation. Although issues in genetics arouse wide public interest, the initial concern about genetic engineering did not come from the public but from scientists actually involved in the research. Genetic material is essentially the same in most living things, and therefore in theory gene transfers can be carried out between any two organisms. In the early 1970s, fears that exploiting this interchangeability could cause the uncontrollable spread of serious disease or damage the environment led some of the first scientists working with gene splicing techniques to raise questions about the unpredictable consequences of their work. For example, one of the

early planned experiments involved attempts to splice SV40, a virus known to cause cancer in mice and hamsters, into a bacterium. What, scientists wondered, would happen if that experimental bacterium was released outside the laboratory and began making billions of copies of itself—and its new cancer-causing gene? The worries were compounded by the fact that the experimental bacterium was closely related to one normally found in human beings. Was it possible that the laboratory bacterium, carrying a cancer virus, might be infectious in humans or cause a cancer epidemic?

Such concerns led in the fall of 1973 and summer of 1974 to the publication, in both Science and Nature, of letters signed by several leading molecular biologists on behalf of those most centrally involved in the field.[7] The first letter called attention to the issues and asked the National Academy of Science to establish a committee, and the second urged scientists to hold off on certain recombinant DNA experiments until the risks could be assessed. This process of assessment was pushed forward by the new NAS committee, chaired by Paul Berg of Stanford University, which organized a meeting in February 1975 at the Asilomar conference center in California. At the meeting were 150 molecular biologists, microbiologists, plant physiologists, industrial researchers, and other scientists from both the United States and abroad, four American lawyers, and a large group of journalists as observers. The Asilomar participants proposed that the self-imposed moratorium be lifted for most recombinant DNA research, subject to specified physical and biological containment measures that would be graduated according to the risk of the experiment.[8]

2. Governmental Supervision. After the meeting, the Director of the National Institutes of Health (NIH) asked the Recombinant DNA Advisory Committee (RAC) that had been established the previous October to consider the Asilomar report and make recommendations. RAC issued guidelines in June 1976 (under the auspices of NIH) for the conduct of recombinant DNA experiments.[9] The guidelines are binding on researchers receiving Federal funds, and--the Commission was informed during this study--the private sector has complied with them voluntarily.

Concern about "biohazards" also found its way to Capitol Hill. Several bills were introduced in the mid-1970s to regulate gene splicing research, although none passed.[10] The political rhetoric of proponents and opponents escalated as the debates moved to the community level; in Cambridge, Massachusetts, and some other localities with major research institutions, concerns about the safety of recombinant DNA experiments aroused loud and often vitriolic public debates.[11] Several communities enacted ordinances restricting gene splicing research.[12]

Meanwhile, RAC became a "second generation" body in which scientific members were joined by a larger representation of public members. As a 25-member body that now meets three to four times a year, it continues to oversee implementation of the NIH guidelines. Those restrictions have been progressively relaxed as scientists have gained experience with the new technology; for most types of experiments, the opponents now bear the burden of proving danger, rather than the proponents having to prove safety.[13]

No physical injuries have been found to have resulted from new organisms created with gene splicing techniques. Most molecular biologists now say they believe that the original worries were exaggerated. Nevertheless, a few scientists continue to maintain that some questions remain unanswered and that continued caution is desirable. This conservative approach influenced RAC enough that the committee decided in early 1982 not to convert the guidelines into a voluntary code of good laboratory practice. Some RAC members also worried that the Federal withdrawal from the field would lead states and localities to adopt varying, and often more onerous, regulations.[14]

3. Deeper Anxieties. While the political, public, and scientific debate has focused on the hazards of pathogenic organisms, it has become apparent that the implications of gene splicing are more far-reaching. The consequences of mistakes or failures in the laboratory have received attention, but success in learning how to manipulate genes could have enormous societal consequences as well. The fact that in the mid-1970s laboratory experiments with recombinant DNA were assumed for a time to be quite risky ought not to mean that forever thereafter any research in gene splicing has to overcome a presumption of danger.[15] Nevertheless, new knowledge does carry a responsibility--often weighty--for its application, and the implications of genetic engineering for new knowledge and novel applications are wide-ranging.

The public's anxiety over genetic engineering may have focused at first--in the wake of press accounts of the Asilomar conference--on biohazards but deeper concerns soon became apparent. In announcing hearings in Cambridge on Harvard's proposed recombinant DNA laboratory in 1976, Mayor Alfred E. Vellucci gave voice to the general disquiet about genetic engineering: "They may come up with a disease that can't be cured--even a monster. Is this the answer to Dr. Frankenstein's dream?"[16]

This "Frankenstein factor"[17] conveys the public uneasiness about the notion that gene splicing might change the nature of human beings, compounded by the heightened anxiety people often feel about interventions involving high technology that rests in the hands of only a few. Indeed, the frequent repetition of the Frankenstein theme by scientists as well as members of the public is quite apt.

Dr. Frankenstein was a creator of new life; gene splicing has raised questions about humanity assuming a role as creator. As a biologist and an eloquent observer of science notes:

> The recombinant DNA line of research is already upsetting, not because of the dangers now being argued about but because it is disturbing in a fundamental way, to face the fact that the genetic machinery in control of the planet's life can be fooled around with so easily. We do not like the idea that anything so fixed and stable as a species line can be changed. The notion that genes can be taken out of one genome and inserted in another is unnerving.[18]

Some scientists were literally unnerved. One leading scientist--who had been an articulate proponent in the 1960s of the hope for improvement that science offered to the "losers" in nature's "genetic lottery"--came to have grave reservations:

> Do we want to assume the basic responsibility for life on this planet--to develop new living forms for our own purposes? Shall we take into our hands our own future evolution?... Perverse as it may, initially, seem to the scientist, we must face the fact that there can be unwanted knowledge.[19]

Dr. Frankenstein's creation was a frightening monster; gene splicing has raised fears about strange new life forms. Some of these--particularly in the popular press--were farfetched:

> Simply put, you take a cell from some plant or animal and extract the chemical (DNA) that governs all the physical and mental characteristics of the whole being. Do the same with another, totally different, plant or animal. Graft the two together, Presto! Shake hands with an orange that quacks, with a flower that can eat you for breakfast--or even with the Flying Nun.[20]

Other concerns with new genetic combinations were more immediate. Some biologists pointed to what they believed are the rigid natural barriers against transfer of genetic material between lower life forms that lack a defined nucleus (such as bacteria) and higher forms (such as plants and animals). Particularly in so-called shotgun experiments, in which the genetic information in an animal cell is broken into many pieces and each is inserted into bacteria so that it will multiply and can be studied, these scientists voiced concern that some of the genetic material might prove very harmful in its new setting even though a risk is not shown, or perhaps does not even exist, when it is part of the total package of genetic material in the original cell.[21]

The Frankenstein story also seems appropriate because the scientist there sought to control his monster, calling to mind the concerns raised about the distribution of power and control associated with gene splicing: "Each new power won _by_ man is a power _over_ man as well."[22] Of equal or greater concern was the view, expressed by some scientists, that even the scientists could not control the "monster." The basic concern about laboratory-generated biohazards lay with a global epidemic from a new pathogen that is resistant to conventional antibiotics or other therapies. As one leading scientist remarked, "You can stop splitting the atom; you can stop visiting the moon; you can stop using aerosols.... But you cannot recall a new form of life."[23] If an organism can find a suitable niche it may survive--and even evolve.

Finally, the Frankenstein analogy comes to mind because of people's concern that something was being done to them and their world by individuals pursuing their own goals but not necessarily the goal of human betterment.

> Working in his dungeon laboratory, Dr. Frankenstein can't be bothered by intruders. He is a genius, he has uncovered the secret of life, and no one can stop his research. Only when his monster begins to destroy does he realize what he has done; and by then it is too late.[24]

Mayor Vellucci of Cambridge voiced what may be a widely held skepticism about researchers when he declared: "I don't think these scientists are thinking about mankind at all. I think that they're getting the thrills and the excitement and the passion to dig in and keep digging to see what the hell they can do."[25] The fear was that for researchers, creating a new life form--even a monster--would be a matter of curiosity; for the public, it would be an assault on traditional values.

Thus, as the laboratory hazards of gene splicing were being contained, concerns about the hazards this technology could pose to human and social values began to bubble to the surface of public awareness. Some scenarios were far-fetched and some fears exaggerated, but in general the concerns did reflect an awareness that a biological revolution with far-reaching implications was taking place. In the Commission's view, there is good reason to attend to these worries, including those that do not involve the sorts of physical hazards that have received most attention thus far. New ideas can change the world in psychological and philosophical terms just as radically as new techniques can change it materially.

Many examples exist of such changes being wrought by the discoveries of science. In the sixteenth century Copernicus showed that the earth revolved around the sun, not the sun around the earth, and thus upset the notion that humanity was at the center of the universe. Similarly, in the last century, the theory of evolution propounded by Charles Darwin challenged the belief that human beings were uniquely created by claiming that they are the biological kin to other living things and that species have slowly differentiated through the undirected agency of natural selection among randomly occurring changes.

The recent work in molecular genetics may again unseat some widely held--if only dimly perceived--views about humanity's place in nature and even about the meaning of being human. Old concepts are already being revised by some scientists, and it cannot be long before the new knowledge and new scientific powers begin to have an impact on general thinking. As a biochemical researcher observed:

> Once we thought the DNA of complex organisms was inscrutable. Now we cope with it readily. We thought of DNA as immovable, a fixed component of cells. Now we know that some modules of DNA are peripatetic; their function depends on their ability to move about....We thought genes were continuous stretches of DNA. Now we know...(they)...may be interrupted dozens of times, and spliced together...when needed.
>
> We have learned that genes are fungible; animal genes function perfectly well within bacteria and bacterial genes within animal cells, confirming the unity of nature. We need no longer depend on chance events to generate the mutations essential for unraveling intricate genetic phenomena.[26]

C. The Commission's Study

Some of the less tangible issues in gene splicing were reflected in the religious organizations' June 1980 letter to the President, which expressed concern that "no government agency or committee is currently exercising adequate oversight or control, nor addressing the fundamental ethical questions (of genetic engineering) in a major way." At its regular meeting in July 1980, the President's Commission took note of this expression of concern and decided to explore the issues through a hearing in September.

At the September 1980 meeting, the Commission heard testimony from scientists, philosophers, and public administrators about ethical, social, and scientific aspects of the subject. The Commission learned that the government's jurisdiction over aspects of genetic engineering is both extensive and diverse. A Commission survey revealed no fewer than 15 government agencies with some involvement or potential involvement in genetic engineering. This includes the conduct and funding of research related to plants, animals, and human beings; authority to regulate the products of gene splicing (for example, drugs) and its by-products (such as occupational and environmental risks); and a range of other activities, including studies of nonhuman implications of genetic technology and an assessment of the role of the United States in the development of the technology worldwide.[27]

Amidst this diversity, however, the common focus of government agencies has been on concrete or practical concerns involving health, environmental, and commercial consequences of the new technology. In deciding to undertake a study of this subject, the Commission specifically excluded the issue of laboratory "biohazards." This reflected the Commission's conclusion that the latter subject was receiving considerable attention and being addressed in both the public and private sector. Morever, it seemed more appropriate for this Commission to examine the broader social and ethical issues in genetic engineering and their significance for public policy.

1. *Objectives.* In exploring those issues, the Commission found that the concerns are heterogeneous to a remarkable degree. Many of them are concrete and practical; others are vague and imprecise. Some are concerns about avoiding undesirable consequences of the technology or achieving its potential benefits, while others reflect uncertainty about whether a particular application of gene splicing is in fact beneficial or undesirable.

The Commission also recognizes that some of the concerns are about future issues that might or might not occur. As discussed in Chapter Two, developments in this field have been swift. Nevertheless, predicting precisely how this technology will develop and how many of its potential applications will be realized is impossible. Direct human applications of gene splicing have only recently begun. Significant technical barriers still impede many potential applications of the technology; sometimes even making progress reveals new hurdles.

Although much remains to be learned in this field, knowledge is being acquired rapidly: in most areas of research, "new" means something that has been found within the past five years; in molecular biology, it often means something found within the past few months. Time and time again in the past ten years, the speed with which events have unfolded has taken well-informed observers by surprise, as noted in a major medical journal:

> While physicians won't be performing gene therapy on humans for some time, that time appears to be approaching more rapidly every day. The tempo of applications of new, basic technologies to clinical medicine continues to be astonishing.[28]

Indeed, prognostications thus far have frequently underestimated the pace of new knowledge.

The most predictable aspect of this technology may be its very unpredictability. The Commission shares the view of the religious leaders, scientists, and others in the media, government, and elsewhere: a continuing exploration is needed of the implications of this technology that has already reshaped the direction of scientific research and that could revolutionize many aspects of life in the modern world.

No attempt is made in this Report to resolve the myriad social and ethical issues generated by the ability to manipulate the basic material of living things. The Commission found that in many instances the issues had not been clearly and usefully articulated yet. A goal of this Report, therefore, is to stimulate thoughtful, long-term discussion--not preempt it with conclusions that would, of necessity, be premature. At this stage in the public discussion, the Commission believes there are at least four broad prerequisites to the development of effective public policy[29]: (1) educating the public about genetics and about the historical context of genetic manipulations; (2) clarifying the concerns underlying the simplistic slogans that are frequently used; (3) identifying the issues of concern in ways meaningful to public policy consideration; and (4) evaluating the need for oversight and analyzing the responsibilities and capabilities for it both within and outside government.

a. Educating the public. The United States is a country with ever-increasing dependence on technological and scientific expertise. Public participation in matters that may have substantial personal import often require a fundamental knowledge of highly specialized fields. Individuals who do not acquire such knowledge may hesitate to participate in the public debate, thinking the subject is too complicated for them and best left to the experts. Alternatively, public discussion can be misguided because people lack understanding of scientific facts and appreciation of the known limits and potentials of a new technology. The issues surrounding genetic engineering face both these problems.

Public policy on genetic engineering will need to draw heavily on the wisdom of "experts" who have earned the public's trust and respect. But an informed public is also an essential element of a democratic decisionmaking process. As emphasized in the Commission's report on screening and counseling for genetic conditions, it is important to include genetics in academic curricula--beginning in early grades.[30] Even with effective formal education on genetics, however, the rapid changes taking place in this field make continuing education essential. This Report seeks to contribute to that process not only by demonstrating the need for enlightened public discussion, but also by providing the reader with some basic background about this new technology.[31] Such a background is important not only for examining significant implications of this technology, but also for distinguishing the issues that merit serious attention from fantastic scenarios that have no scientific basis.

The Commission also finds a second type of information related to gene splicing important for public discussions--an understanding of the context in which this new technology arises. Gene splicing is a revolutionary scientific technique that recasts past ideas and reshapes future directions. Even so, it does not necessarily follow that all its applications or objectives represent a radical departure from the past. Indeed, the question of whether this application differs in significant ways from previous interventions or capacities served as an important guidepost for much of the Commission's discussion of social and ethical concerns about genetic engineering. For example, do the partnerships emerging between industry and academia in regard to gene splicing differ from past interactions in ways that give rise to new concerns or require unique responses? Would replacing a defective gene with a normal one from another person to correct a blood disorder differ socially and ethically from current investigations in which bone marrow is transplanted from one person to another for the same purpose? The Commission attempts to bring this perspective to its discussion of the issues.

b. Clarifying concerns expressed in slogans. A complex and seemingly mysterious new technology with untapped potential is a ready target for simplistic slogans that try to capture vague fears. This is very much the case with genetic engineering. In Chapter Three, the Commission examines some of the slogans that have been invoked on both sides of the genetic engineering controversy, and attempts to clarify and analyze the concerns they seem to reflect.

A recent public opinion poll, for example, found that the single area of research in which restraint on scientific inquiry was favored is "creation of new life forms."[32] But what is meant by this term? Is bacteria into which a human insulin gene has been inserted a "new life form" that ought not to be created? Is a new hybrid corn offensive? Or is the fear of a new life form really about partially human hybrids?

Concern is also expressed about gene splicing because it will cause human beings to "control evolution" or lead to "an alteration of the gene pool." But humanity's activities have always affected the gene pool. And why would tinkering with genes mean that evolution has been "controlled"?

On the other hand, arguments in favor of caution and control are sometimes met with claims of "academic freedom." What application does this principle have in discussing physical risk to other people? And how ought the value of the pursuit of knowledge be weighed against other values?

c. Identifying the public policy issues. The diversity of social and ethical issues implies the need for similarly varied responses. A third objective of this Report, therefore, is to organize these issues in a way that is useful both for general understanding and for the formulation of sound public policy. The Commission has focused on the various types of uncertainties associated with the uses of gene splicing techniques: evaluative or ethical uncertainty; conceptual uncertainty; and occurrence uncertainty.

The first type of uncertainty occurs when no societal consensus exists as to whether certain applications of gene splicing are beneficial or undesirable. Should research be conducted to generate means by which "positive" traits could be introduced into a person genetically--for example, by improving memory? Would this be regarded as a socially and ethically desirable application of the technology? Further uncertainty occurs because the determination of what constitutes a "defect" or "disease" varies over time and between cultures.

Conceptual uncertainty refers to the fundamental change in concepts that this new technology can engender. As noted earlier, the notion that genes, once conceived of as fixed, can now be manipulated and exchanged has been described as "unnerving." The significance of this for people's conception of their role in the universe and even for the meaning of being human underlie an important set of concerns.

Concerns like these have not typically arisen in public policy discussions. A limited number of implications of gene splicing, however, do echo issues raised by other technologies that have prompted generally uncontroversial public policy responses. The premarket testing of new drugs is one example. A consensus exists that certain outcomes would be beneficial, such as the development of safe, effective drugs, and others harmful, such as unsafe, ineffective drugs. The uncertainty involved is whether a particular outcome will occur. Policy can be directed specifically at promoting the desirable outcomes and minimizing the likelihood of harmful effects.

Occurrence uncertainty also applies to some issues that cannot be so readily addressed. As with many new technologies, the full range of scientific effects of gene splicing cannot now be predicted with complete certainty. And those effects will be expressed in a future that cannot be known in advance.

Decisions made about the future of this technology and its applications will need to be made with reference to the varied types of risks and uncertainties at stake in gene splicing. Chapter Three attempts to organize the issues in ways that will foster the development of effective public policy.

d. Evaluating the need for oversight. Having set out the types of risks posed by gene splicing, the Commission then considers the need for oversight of these issues. A variety of mechanisms, involving both the government and the private sector, are possible. One common feature unites all those that seem appropriate to the Commisson: they draw on, but are not controlled by, gene splicing experts.

2. The Process of Study. At its July 1980 meeting, the Commission decided that its initial response to the religious leaders' concerns about government oversight would be to survey governmental agencies about their activities in this field. With the aid of a special consultant, a review of the field was also prepared for the Commissioners.

A portion of the September 1980 meeting was devoted to reports by representatives of the most actively involved Federal agencies. In addition, the scientific prospects for, and ethical implications of, the use of genetic engineering in human beings were discussed by several invited witnesses. The Commission decided at that time to add this study to those mandated, according to its statutory authority to do so.[33] During the following two years, the issue was discussed by the Commission at a number of its meetings.

To assist in preparing this Report, the Commission assembled a diverse panel that included representatives from medicine and biology, philosophy and ethics, law, social policy, and the private industrial sector.[34] These consultants held a series of meetings with Commissioners and staff on the direction of the Commission's work in this area and the issues to be addressed. A preliminary analysis of the issues was prepared for discussion by the Commission in July 1981. This and subsequent drafts were submitted to some members of the panel, and comments were also received from other scientists and expert observers of the developments of genetic engineering.

Several knowledgeable people were invited to discuss the draft Report with the Commissioners at a hearing on July 10, 1982, at which time preliminary approval was given to a portion of the Report, subject to a number of suggested changes and additions. A revised draft was reviewed by the Commission at its November 12, 1982, meeting and approved, subject to several editorial changes.

FOOTNOTES

1. The full text of the letter from the religious bodies appears as Appendix B at pp. ___ - ___, infra.

2. For definitions of the technical terms used throughout this Report, see Glossary, Appendix A, at pp. ___ - ___ infra.

3. A discussion of genetic screening can be found in the Commission's report, Screening and Counseling for Genetic Conditions, U.S. Government Printing Office, Washington (1982).

4. Rollin D. Hotchkiss, Portents for a Genetic Engineering 56 J. Heredity 197 (1965).

5. In vitro fertilization (IVF) is a technique for achieving fertilization of an egg outside of the body, in a laboratory dish (from the Latin, in vitro, for "in glass"). In its therapeutic uses it also encompasses embryo transfer to a uterus. One or more eggs are surgically removed from an ovary of a woman with obstructed Fallopian tubes, fertilized with her husband's sperm in a laboratory dish, allowed to develop there for a few days, and then transferred into the woman's uterus, where the pregnancy proceeds. IVF has received a great deal of publicity in the past few years as some previously infertile women have given birth following the use of this technique. The Commission decided in May 1980 not to take up the subject of human in vitro fertilization because the Ethics Advisory Board of the Department of Health and Human Services had studied the subject at length. Action has not yet been taken on the EAB's May 4, 1979, report and recommendations to the Secretary.

6. Cloning, the production of genetically identical copies, can apply to cells or whole organisms. Although the idea of creating clones in the laboratory is new, many species of plant and animals, including humans, produce natural clones. For example, identical twins, triplets, etc., are members of a clone, since they are derived from the same fertilized egg.

In 1981 researchers produced a clone of mice from embryonic cells. Nuclei taken from a seven-day-old embryo were inserted into newly fertilized mouse eggs from which the nuclei had been removed. Jean L. Marx, Three Mice "Cloned" in Switzerland, 211 Science 375 (1981). These eggs were then implanted into the uterus of "foster mothers" who subsequently gave birth to genetically identical mice. The success demonstrated that the embryonic cells retain their totipotency (that is, their ability to develop into a complete mouse). Developing a clone from an existing individual, rather than embryonic cells, is more difficult since these cells have already differentiated and would need to regain totipotency.

In light of the public attention cloning has received, it is important to emphasize that even if a cell from a developed organism could produce a clone, it would not result in an instantaneous "carbon copy" of the original. In cloning, the genetic material is inserted into a recently fertilized egg to produce a new generation with the same genetic makeup. The technology to clone a human does not--and may never--exist. Moreover, the critical nongenetic influences on development make it difficult to imagine producing a human clone who would act or appear "identical."

7. Maxine Singer and Dieter Soll, *Guidelines for DNA hybrid molecules* (Letter), 181 Science 1114 (1973); *Paul Berg et al., Potential biohazards of recombinant DNA molecules* (Letter), 185 Science 303 (1974). Taking as his starting point the recombinant DNA experience, a leading ethicist has argued for an expanded vision of scientific responsibility:

> If the essence of good scientific research is to leave no stone unturned, it is no less pertinent to moral thought. A scientific researcher would, in strictly scientific terms, be considered poor if he did not allow his mind to roam in all directions during the phase of hypothesis development, taking seriously any idea that might produce a promising lead....The same is true of moral thinking, particularly when it bears on the future consequences of our actions. We are obliged to explore all possibilities, however vague and remote; and the moral person will also end by throwing most of them out--most, finally, but not all. Since we surely now know that scientific research, whether basic or applied, is a source of enormous power for both good and ill, the scientific researcher has, then, an obligation to be as active in his moral imagination as in his scientific imagination. We ask the same of any person in a position of power.

Daniel Callahan, *Ethical Responsibility in Science in the Face of Uncertain Consequences*, 265 Ann. N.Y. Acad. Sci. 1,6 (1976).

8. Michael Rogers, Biohazard, Alfred A. Knopf, New York (1973) at 51-101; William Bennett and Joel Gurin, *Science that Frightens Scientists*, The Atlantic 43, 49-50 (Feb. 1977); Roger B. Dworkin, *Science, Society, and the Expert Town Meeting: Some Comments on Asilomar*, 51 S. Cal. L. Rev. 1471 (1978).

9. 41 Federal Register 27902 (July 7, 1976).

10. A total of 16 bills related to recombinant DNA research were introduced in the 95th Congress, in addition to numerous proposed bills that were considered but never formally introduced. For a listing of the bills see National Institutes of Health, Recombinant DNA Research Volume 2, Documents Relating to "NIH Guidelines for Research Involving Recombinant DNA Molecules" June 1976-November 1977, U.S. Department of Health, Education and Welfare, Washington (1978).

11. Nicholas Wade, The Ultimate Experiment, Walker and Company, New York (1977) at 127-41.

12. The Cambridge statute incorporates by reference the RAC guidelines (applying them to industry as well as universities) and established a Cambridge Biohazards Committee for oversight. Between 1977 and 1979 New York and Maryland and five towns, from New Jersey to California, followed the Cambridge model; in 1981 and 1982 a second wave of legislation was

enacted in several communities in the Boston area addressed specifically to the commercial uses of recombinant DNA technology. Sheldon Krimsky, *Local Monitoring of Biotechnology: The Second Wave of Recombinant DNA Laws*, 5 Recombinant DNA Technical Bull. 79 (1982). *See also* Cambridge, Mass. Ordinance 955, Ordinance for the Use of Recombinant DNA Technology in the City of Cambridge (April 2, 1981); Waltham, Mass. General Ordinances ch. 22 (1981); Michael D. Stein, *Boston Strikes Out: Local DNA Guidelines*, 292 Nature 283 (1981).

13. To suggest that the "burden of proof" issue lies at the heart of the recombinant DNA debate is not to suggest that it is a single issue or, indeed, that one determination of *who* bears *what* burden of going forward with *what* evidence and persuading *whom* will be satisfactory for all aspects of public policy regarding recombinant DNA. One ground for suggesting different burdens might be that the risks motivating concern in the first place are of different sorts [*i.e.*, physical versus social risks]. Another way of slicing the conceptual pie is according to the stage of the research process, between the risks of *means*... and the risks of *ends*.

A.M. Capron, *Prologue: Why Recombinant DNA?*, 51 S. Cal. L. Rev. 973, 977 (1978).

14. Marjorie Sun, *Committee Votes to Keep DNA Rules Mandatory*, 215 Science 949 (1982).

15. It is generally true that scientific researchers need not demonstrate the safety of their investigations as a condition of proceeding. But can review be triggered by the expression of genuine concern about risks by knowledgeable parties? In the case of recombinant DNA, do the initial warnings by scientists of possible disasters from research mishaps have continuing force once the same scientists suggest that subsequent experience has led them to doubt that any unusual risk exists? In other words, once triggered can a process of decision be called off by anything short of a judgment on the merits?

Capron, *supra* note 13.

16. John Kifner, *"Creation of Life" Experiment at Harvard Stirs Heated Dispute*, N.Y. Times, June 17, 1976, at A-22.

17. Willard Gaylin, *The Frankenstein Factor*, 297 New Eng. J. Med. 665 (1977).

18. Lewis Thomas, *The Hazards of Science*, 296 New Eng. J. Med. 324, 326 (1977).

19. Bernard Dixon, *Tinkering with genes*, 235 Spectator 289 (1975) (quoting Robert L. Sinsheimer, Chairman, Department of Biology, Caltech).

20. Susan Carson, *New Origin of Species*, Winnipeg Tribune, July 2, 1979, Canadian (Magazine), at 2.

21. Erwin Chargaff, On the Dangers of Genetic Meddling (Letter), 192 Science 938 (1976).

22. C. S. Lewis, The Abolition of Man, Collier-Macmillan, New York (1965) at 71.

23. Charles A. White, It's not nice to fool with mother nature, 43 Canada & the World 10, 11 (1977) (quoting Erwin Chargaff, a biochemist at Columbia University). Professor Chargaff also asked "[H]ow about the exchange of genetic material [among microorganisms] in the human gut? How can we be sure what would happen once the little beasts escaped from the laboratory?" Chargaff, supra note 21, at 939.

24. Arthur Lubow, Playing God with DNA, 8 New Times 48, 61 (Jan. 7, 1977).

25. Id.

26. Maxine Singer, Recombinant DNA Revisited (Editorial), 209 Science 1317 (1980).

27. The results of the survey appear as Appendix C at pp. _____ - ______ infra.

28. Lawrence D. Grouse, Restriction Enzymes, Interferon, and the Therapy for Advanced Cancer, 247 J.A.M.A. 1742 (1982).

29. The Commission uses the term "public policy" broadly to include not only formal laws and regulations but the many programs and policies of individuals and institutions that society decides are acceptable and not in need of direct collective intervention. Public policy is not limited to situations where the government has taken action; indeed, as the Report notes, the Commission concludes that many issues raised by genetic engineering are not proper subjects of government regulation, which is itself a public policy judgment.

30. Screening and Counseling for Genetic Conditions, supra note 3, at _________.

31. Chapter Two provides technical descriptions of the recombinant DNA process, describes the "state of the art," and offers some perspective on gene splicing's potential and limitations. This information is intended to provide the necessary scientific groundwork for an understanding of the social and ethical concerns and the public policy considerations.

32. John Walsh, Public Attitude Toward Science Is Yes, but-, 215 Science 270 (1982).

33. 42 U.S.C. § 300v-1(a)(2).

34. For a list of the panel members, see Appendix D, pp. xx-yy infra.

CHAPTER 2: THE DAWN OF A NEW SCIENTIFIC ERA

Many of the questions raised about genetic engineering cannot be explored without some understanding of the technical aspects of contemporary genetics and cell biology. Lack of information--or misinformation--not only provokes unwarranted fears but may even mean that legitimate and important questions remain unasked. Yet most Americans have had little formal training in biology, let alone in the specialized fields, such as micro- and molecular biology, that are involved in genetic engineering. Although a brief synopsis is plainly no substitute for a detailed education, some background may be helpful for nonspecialist readers. This chapter of the Report is intended, then, to explain a few essential concepts, to describe several of the most important techniques of genetic engineering, and to show how rapidly this field is moving toward direct human applications.

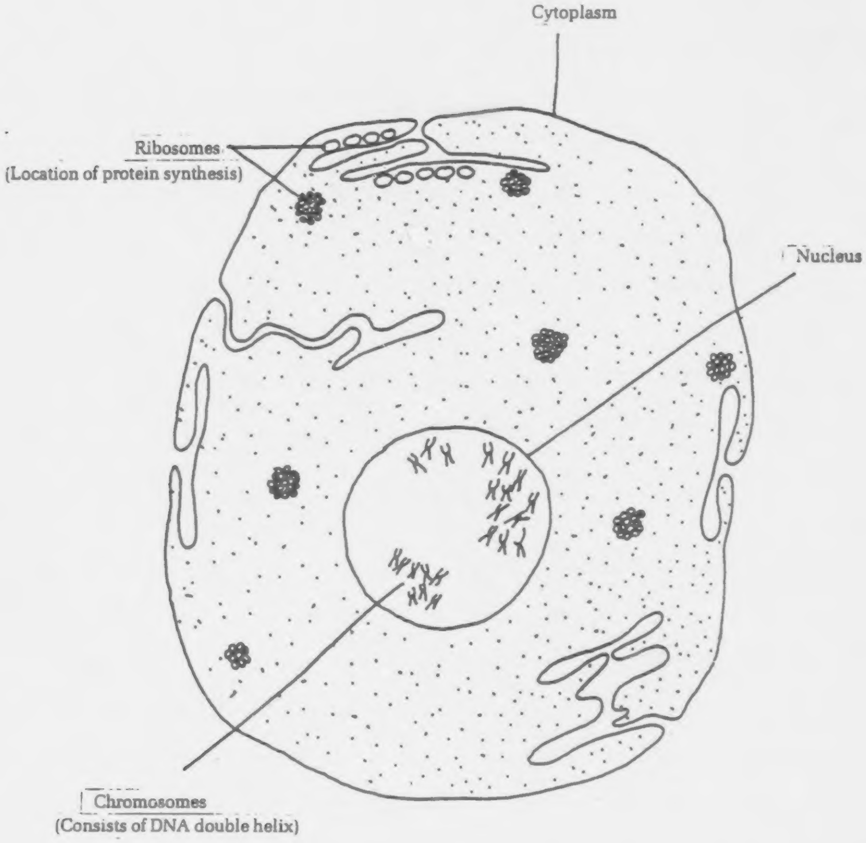
A. Discovering Life's Mysteries

What is remarkable about the science of gene splicing is not that it seems strange to laypeople--for all science is arcane to those who do not specialize in its study--but rather how unfamiliar it would be for the geneticists of even one generation ago. The existence of discrete inherited factors (later called genes) was postulated in 1865 by Gregor Mendel, a Moravian abbot who studied the patterns of inheritance in pea plants; his important work relied, however, on inferences about genes, not knowledge about their structure or functioning. Mendel's work lay forgotten until the beginning of this century, when the techniques of classical genetics were developed and physicians began to apply genetic knowledge in diagnosing conditions and in advising people about the conditions known to follow Mendelian patterns. Fifty years passed until Francis Crick and James Watson proposed the double helix as the structure for deoxyribonucleic acid (DNA), which is sometimes called the "master molecule of life" since almost all living things--including plants, animals, and bacteria--possess it. And the basic technique of gene splicing--a method for cutting and reuniting DNA--is itself only a decade old.[1]

Equally remarkable is that many new discoveries point to further unanswered--and perhaps even unanticipated--questions. The humbling reality of human ignorance is as relevant for those in industry and government who sponsor and regulate scientific research as it is for those who engage in that research. Any attempt to unravel more of life's mysteries can lead in unexpected directions, with unknown risks and benefits. The choices made about proceeding in one direction rather than another--or whether to proceed at all--are not simply matters of original scientific insight or intuition nor even of taking the "next logical scientific step." They also depend upon the judgment of individual scientists, laboratory directors, and public and private sector sponsors, drawing on analogy and conjecture, educated by experience, and reflecting personal and institutional values.[2]

1. Cells and Genes. The human body is made up of billions of cells. Each cell has a particular function--cells in the gastrointestinal tract produce enzymes that digest food, bone cells provide structural support, and so forth. In spite of their markedly varied functions, most cells share the same structural organization--they have a nucleus, where the genetic information is stored, and cytoplasm, where the specialized products of the cell are made (see Figure 1).

Figure 1: Cell Structure



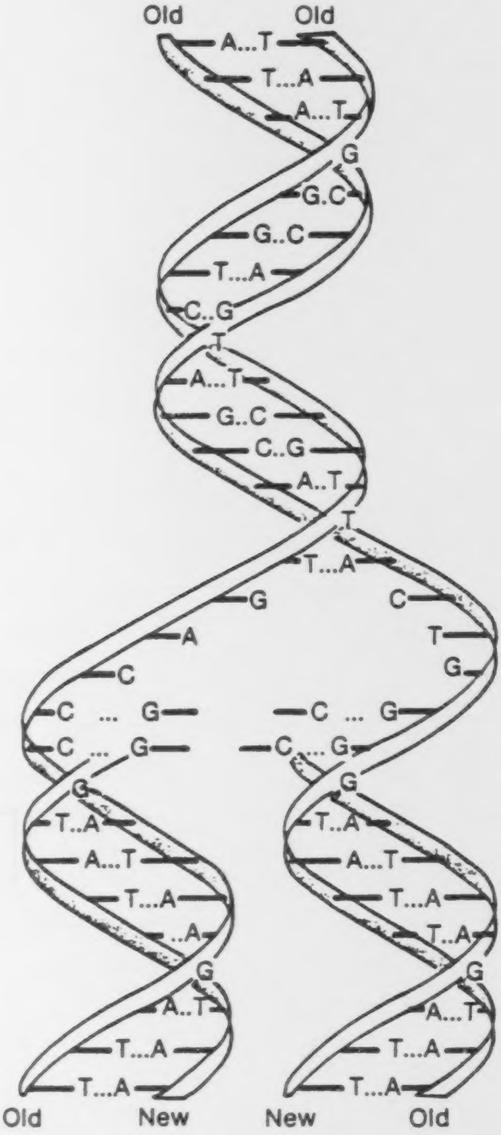
Cytoplasm
Ribosomes
(Location of protein synthesis)
Nucleus
Chromosomes
(Consists of DNA double helix)

It has been thought that all cells in an organism normally contain exactly the same genetic information, with the exception of the germ cells (sperm and eggs), which carry only half. This information is located on individual packets called chromosomes, which come in pairs, half derived from each parent. Every species of plant or animal has a characteristic number of chromosomes. Humans usually have 23 pairs, or a total of 46; the germ cells have 23 chromosomes, one from each pair, while the somatic cells (the rest of the cells in the body) contain a full set of chromosomes. Recent studies have shown that the genetic information is rearranged in some cells; thus far, these findings are limited to the antibody-producing cells.[3]

Each chromosome includes a long thread of DNA, wrapped up in proteins. DNA is made up of chemicals called nucleotides, consisting of one small sugar molecule, one phosphate group, and one of four nitrogenous bases, which can be thought of as the four letters in the genetic alphabet (A, G, T, and C).[4] DNA consists of two strings of nucleotides lined up next to each other like two sides of a zipper--the phosphates and sugars forming the ribbons and the nitrogenous bases acting like the interlocking teeth. The two strands are twisted around each other in a spiral fashion, forming what Crick and Watson in 1953 labeled a double helix. Each nucleotide is matched with another, to form a pair. That is, the two sides of the zipper can fit together in only one way: A paired with T, and G with C.

When a cell divides into two daughter (or progeny) cells--a process called replication--a complete and faithful copy of the genetic code stored on each chromosome is usually transmitted to each daughter cell. Each half of the zipper acts like a template for the creation of its zipper-mate by drawing to itself free nucleotides, which then line up according to the A-T and G-C pattern (see Figure 2).

Figure 2: Replication of DNA


Old
Old
A...T
T...A
A...T
G
G.C
G..C
T...A
C..G
T
A...T
G..C
C..G
A..T
T
T...A
G
C
A
T
C
G
C ... G
C ... G
C ... G
C....G
G
G
T..A
T..A
A...T
A...T
T...A
T...A
..A
T..A
G
G
A...T
A...T
T...A
T...A
T...A
T...A
Old
New
New
Old

When DNA replicates, the original strands unwind and serve as templates for the building of new complementary strands. The daughter molecules are exact copies of the parent, with each having one of the parent strands.

SOURCE: Office of Technology Assessment.

Not all the DNA in chromosomes seems to have a function. The portions with the coded instructions to the cell to perform a particular function (usually to manufacture one particular protein) are called genes. Within the gene are the actual coding regions (called exons), between which are DNA sequences called introns. Genetic information is transferred from the DNA in the nucleus to the cytoplasm by RNA (ribonucleic acid), which is a copy of one strand of the DNA. During this transfer, the introns are spliced out of the RNA. The resulting RNA messengers pass through the cell's protein-synthesizing machinery (called ribosomes), like a punched tape running through a computer to direct a machine's operation.

Proteins—the hormones, enzymes, connecting material, and so forth that give cells and organisms their characteristics--are made up of amino acids. The information carried by the RNA determines how the amino acids combine to make specific proteins. There are 20 amino acids, each one determined by a specific combination of three of the nucleotide "letters" into a "codon." On average, each gene contains slighty more than 300 codons.

Although all cells in an organism carry basically the same genetic material in their nuclei, the specialized nature of each cell derives from the fact that only a small portion of this genetic material (about 5-10%) is active in any cell. In the process of developing from a fertilized egg, each type of cell switches on certain genes and switches off all the others. When "liver genes" are active, for example, a cell behaves as a liver cell because the genes are directing the cytoplasm to make the products that allow the cell to perform a liver's functions, which would not be possible unless all the genes irrelevant to a liver cell, such as "muscle genes," were turned off.

2. Accidents and Diseases. Occasionally--perhaps because of an

error that occurs for some unexplained reason when the cell replicates or because of an outside influence such as a virus or radiation--the specific sequence in a DNA molecule is altered by a change of one or more nucleotides. Such a change is called a mutation. If a mutation occurs in a gene that is active in that cell, the cell will produce a variant protein, as will its daughter cells since they will inherit the same mutation. If other cells of the same type continue to perform their functions properly, the existence of a small amount of variant protein will usually have no adverse effects on the individual. Some mutations, however, are very harmful; for example, a defective protein can be lethal, or a malignant tumor can result from a mutation that alters a gene in a single somatic cell.

Mutations that occur in somatic cells only affect the progeny of that mutant cell, so that the effects of such mutations are restricted to the individual in whom they occur. In the germ cells, however, mutations result in the altered DNA being transmitted to all cells--somatic and germinal--of an offspring. Inherited mutations that result in deleterious effects are termed genetic diseases. Even though an inherited mutation is present in the DNA sequence of all the body cells, it only affects the function of those specialized cells that manufacture the defective product. For example, a mutation in the gene for rhodopsin (a protein necessary for vision) may result in color blindness, but since the gene is only active in cells in the eye it has no other known effects on a color-blind individual.

B. The Technology of Gene Splicing

Gene splicing techniques have been understood by scientists for only a decade. During that time, they have been used primarily in microorganisms. Though experiments with higher animals indicated the possibility of using gene splicing for human therapy and diagnosis, numerous hurdles had to be crossed before such steps could be taken. Recent research has cleared some of those hurdles, and work is under way that may conquer the rest much sooner than was thought possible even two years ago, when the Commission began this study.

1. Recombinant DNA Techniques. It was once thought that genetic material was very fixed in its location. Recent findings demonstrate that genetic recombination (the breaking and relinking of different pieces of DNA) is more common between and within organisms--from viruses and bacteria to human beings--than scientists realized. In fact, genetic exchange is a mechanism that may, in evolutionary terms, account for the appearance of marked variations among individuals in a given species.[5]

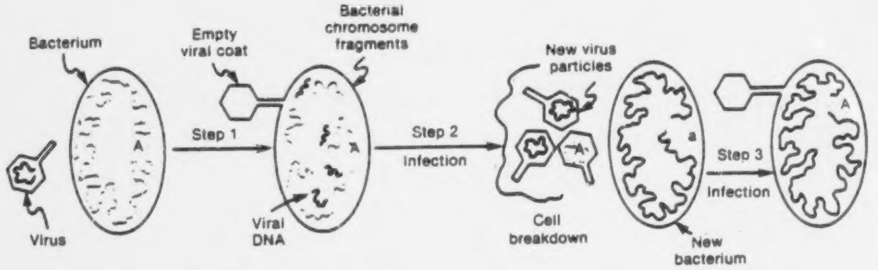
If DNA replication were the only mechanism for the transfer of genetic information, every single bacterium would have the same properties. In fact, three general mechanisms of genetic exchange occur commonly in bacteria.[6] The first, termed transduction, occurs when the genetic material of a bacteriophage (a virus that infects bacteria) enters a bacterium and replicates; during this process some of the host cell's DNA may be incorporated into the virus, which carries this DNA along when it infects the next bacterium, into whose DNA the new material is sometimes then incorporated (see Figure 3).

In a second process, called conjugation, bacterial DNA is transferred directly from one microorganism to another. Some bacteria possess plasmids, small loops of DNA separate from their own chromosome, that give the bacteria the ability to inject some of their DNA directly into another bacterium (see Figure 4). And third, bacterial cells can also pick up bits of DNA from the surrounding environment; this is called transformation.

These mechanisms--naturally occurring forms of gene splicing--

Figure 3

Transduction: The Transfer of Genetic Material in Bacteria by Means of Viruses

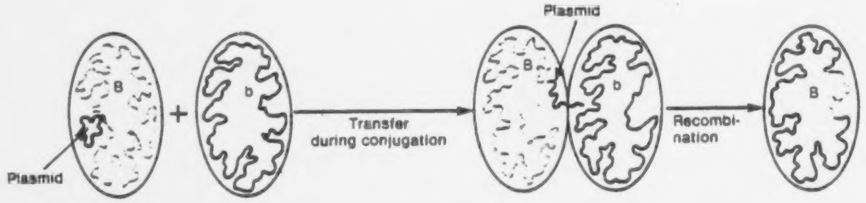

Bacterium
Empty viral coat
Bacterial chromosome fragments
New virus particles
Step 1
Step 2
Infection
A
a
Step 3
Infection
A
Virus
Viral DNA
Cell breakdown
New bacterium

In step 1 of viral transduction, the infecting virus injects its DNA into the cell. In step 2 when the new viral particles are formed, some of the bacterial chromosomal fragments, such as gene A, may be accidently incorporated into these progeny viruses instead of the viral DNA. In step 3 when these particles infect a new cell, the genetic elements incorporated from the first bacterium can recombine with homologous segments in the second, thus exchanging gene A for gene a.

SOURCE: Office of Technology Assessment.

Figure 4

Conjugation: The Transfer of Genetic Material in Bacteria by Mating


Plasmid
B
+
b
Transfer during conjugation
B
b
Recombination
B
Plasmid

In conjugation, a plasmid inhabiting a bacterium can transfer the bacterial chromosome to a second cell where homologous segments of DNA can recombine, thus exchanging gene B from the first bacterium for gene b from the second.

SOURCE: Office of Technology Assessment.

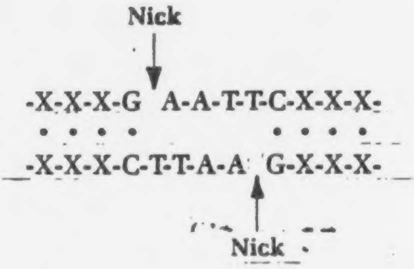
permit the exchange of genetic material among bacteria, which can have marked effects on the bacteria's survival. The rapid spreading of resistance to antibiotics, such as the penicillin-resistance in gonorrhea bacteria and in Hemophilus influenzae (the most frequent cause of children's bacterial meningitis), documents the occurrence of genetic transfers as well as their benefit, from a bacterial standpoint.

The basic processes underlying genetic engineering are thus "natural" and not revolutionary. Indeed, it was the discovery that these processes were occurring that suggested to scientists the great possibilities and basic methods of gene splicing. What is new, however, is the ability of scientists to control the processes. Before the advent of this new technology, genetic exchanges were more or less random and occurred usually within the same species; now it is possible to hook together DNA from different species in a fashion designed by human beings.

The key to human manipulation of DNA came with the discovery, in the early 1970s, of restriction enzymes.[7] Each restriction enzyme, of which about 150 have so far been identified, makes it is possible to cut DNA at the point where a particular nucleotide sequence occurs. The breaks, which are termed "nicks," occur in a staggered fashion on the two DNA strands rather than directly opposite each other. Once cut, in this fashion, a DNA strand has "sticky ends"; the exposed ends are ready to "stick" to another fragment that has been cut by the same restriction enzyme (see Figure 5). Once the pieces are "annealed" and any remaining gaps are ligated, the "recombinant DNA" strand will be reproduced when the DNA replicates.

Recombinant DNA studies have been performed primarily in laboratory

Figure 5: Creation of "Sticky Ends" by a Restriction Enzyme

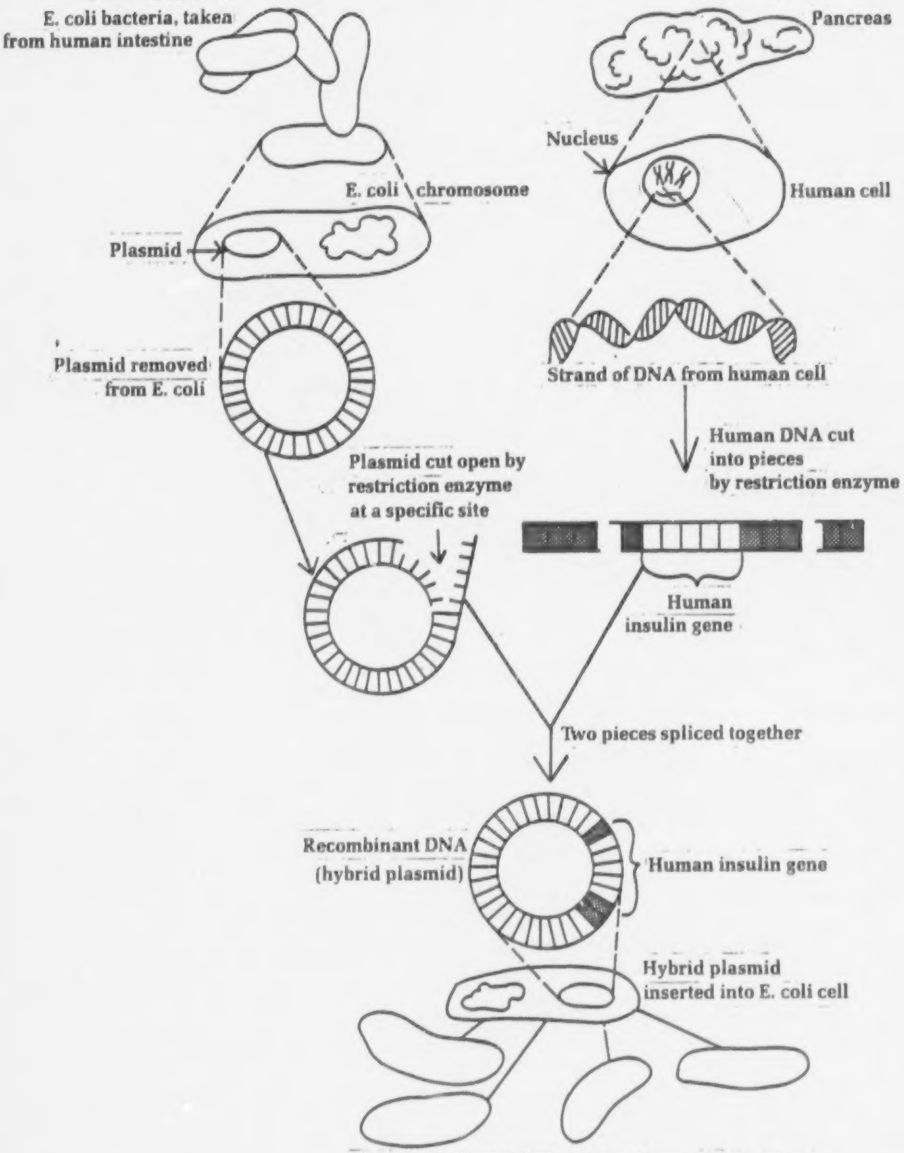


One restriction enzyme produced by *E. coli*, named Eco RI, recognizes the DNA sequence -G-A-A-T-T-C- on one strand and -C-T-T-A-A-G- on the other. It does not cut clearly across the two strands, however, but between the G and A on both strands, leaving each with exposed bases that can stick to another DNA strand that has been cut in the same fashion and also has an exposed -A-A-T-T- sequence.

strains of the bacterium *Escherichia coli*, which is normally present in the human intestine. This bacterium possesses only one small chromosome, but it may also contain several ring-shaped plasmids. Plasmids turn out to be useful vehicles (or vectors) by which a foreign gene can be introduced into the bacterium. A plasmid can be broken open with restriction enzymes, and DNA from another organism (for example, the gene for human insulin) can then be spliced into the plasmid (see Figure 6). After being resealed into a circle, the hybrid plasmid can then be transferred back into the bacterium, which will carry out the instructions of the inserted DNA (in this case, to produce human insulin) as if it were the cell's own DNA. In addition, since plasmids contain genes for their own replication independent of bacterial DNA replication, many copies of the hybrid plasmid will be present in each *E. coli* cell. The end result is a culture of *E. coli* containing many copies of the original insulin gene and capable of producing large amounts of insulin.

The process of isolating or selecting for a particular gene is commonly called cloning a gene. A clone is a group all of whose members are identical. Theoretically, this technology allows any gene from any species to be cloned, but at least two major steps must be taken to make use of this technology. First, it is quite easy to break apart the DNA of higher organisms and insert fragments randomly into plasmids--a so-called shotgun experiment--but identifying the genes on these randomly cloned pieces or selecting only those recombinant molecules containing a specific gene is much more difficult. Because scientists do not yet fully understand what controls gene regulation, inducing expression of the inserted genes has been a second major hurdle. Recently, scientists have been successful in getting a recombinant

Figure 6: Splicing Human Gene into Plasmid


E. coli bacteria, taken from human intestine
Pancreas
Nucleus
E. coli chromosome
Human cell
Plasmid
Plasmid removed from E. coli
Strand of DNA from human cell
Human DNA cut into pieces by restriction enzyme
Plasmid cut open by restriction enzyme at a specific site
Human insulin gene
Two pieces spliced together
Recombinant DNA (hybrid plasmid)
Human insulin gene
Hybrid plasmid inserted into E. coli cell

Bacteria with hybrid plasmid replicate, creating clone capable of producing insulin gene to function in multicell animals and, with the discovery of what are termed transposable elements, even in correcting a defect in some fruit flies' genes.[8] This development serves as a reminder that many technical barriers that loom large are rapidly overcome. Of course, new knowledge sometimes also reveals further, unanticipated technical difficulties to be overcome.

2. Cell Fusion. Cutting apart DNA chains is not the only way that scientists can transfer genetic material from one cell to another. Cell fusion, which involves the breaking down of cell membranes and the merging of two different types of cells, can also be regarded as a form of genetic engineering although it does not involve direct manipulation of DNA segments. It is being vigorously explored by biomedical scientists who are attempting to map the specific location of human genes on chromosomes and to learn about cellular development and differentiation. These advances should ultimately lead to better understanding, diagnosis, and treatment of various diseases and cancers.

For example, researchers can now produce what are termed monoclonal antibodies. Antibodies are substances produced by the body to fight foreign substances, such as microbial "invaders." Unlike other methods of production, cell fusion techniques have provided especially pure antibodies against a particular invader (or "antigen"). They are called monoclonal because they are produced by a clone of cells descended from a single fabricated original. First, scientists stimulate a mouse to produce antibodies by injecting it with a protein. White blood cells containing an antibody aimed at fighting the "disease" (which is how the mouse's immune system regards the injected proteins) are then fused chemically with malignant cells through a process that involves dissolving and regenerating the cells' outer membranes. This combination--called a hybridoma--inherits the cancer cells' ability to proliferate rapidly and indefinitely and the blood cells' capacity to produce the antibody. Scientists can thus generate a huge clone of cells, which can provide a large amount of the desired antibody.

Cell fusion is not limited to the creation of hybridomas. The 1980 Supreme Court decision that sanctioned the patenting of "new life forms" did not involve recombinant DNA techniques but rather the insertion into bacteria of four naturally occurring plasmids capable of degrading four components of oil.[9] The Court held the resulting microorganism was patentable because it was new (as bacteria in nature did not incorporate all four of the plasmids at once) and useful (as the genetically engineered bacteria could break down oil spills more rapidly and efficiently).

C. Genetically Engineered Medical Products

The ability to "engineer" new capabilities into microorganisms has now been used to develop therapeutic and diagnostic agents for human use. This is the first, and thus far the major, use of gene splicing in the medical sphere.

1. Production of Drugs and Biologics. Most living cells are protein factories, "manufacturing" products according to the "code" of those genes in the cells that are active. Through the use of gene splicing techniques, bacterial cells can be altered so that they will turn out the product encoded by a foreign gene that has been spliced into a plasmid in the bacteria. When such bacteria are then grown in large-scale fermentation broths, huge quantities of valuable medical products are expected to be harvested because bacteria multiply very rapidly--a single bacterium can produce more than a billion copies of

itself in 15 hours.

The list of medically useful products that may be obtained through gene splicing techniques is long; a few applications will serve to illustrate. The new technology has already led to the production of several useful human hormones, including human growth hormone to treat dwarfism. To date, many desirable medical products had to be isolated and purified biochemically from natural sources. For example, the insulin consumed by diabetics in this country is isolated from the pancreata of over 80 million cows and pigs each year. Since the supply of pancreas glands is dependent on the demand for beef and pork, gene splicing offers a more stable supply of this essential hormone. Insulin produced with recombinant DNA methods has recently been approved for sale in Great Britain and the United States.[10]

It is predicted that gene cloning of many human hormones will soon be accomplished. Other useful products made by the human body in small quantities are being worked on. For example, there is interest in producing urokinase, which dissolves blood clots and may be useful for treating thrombophlebitis, and anti-hemophilic factor, which is required for blood clotting and is needed by hemophiliacs.

Interferon is another natural product that has attracted much interest for its apparent ability, discovered in 1957, to prevent a virus from proliferating after it invades a body. By the mid-1970s, laboratory evidence suggested that interferon might curtail the spread of certain cancers. Clinical tests and therapeutic application proceeded slowly, however, because supplies of interferon were very limited and extremely costly. Most interferon was extracted from cells of donor blood samples in minute quantities, usually laced with impurities. The cost of treating one cancer patient is between $20,000 and $30,000. Therefore, great enthusiasm greeted the prospect of using recombinant DNA techniques to create interferon (a process that also revealed that interferon is not a single substance but a family of related ones, each of which may be effective against certain problems).[11]

Interferon produced through gene splicing is now being tested in clinical trials. Although research to date on interferon obtained by the traditional methods suggests that its potential as the proclaimed "wonder drug" was greatly overstated, the use of gene splicing to produce pure samples in larger quantities offers an opportunity to clarify the many questions that have arisen in the limited existing clinical tests and to resolve some of the issues regarding the use of human interferon in cancer treatment.

Another area of widespread applicability is in the production of useful vaccines. Presently, a weakened strain of a virus must be grown in tissue culture, a tedious chore, and then inoculated into humans. There is always a risk that the virus used for inoculation may change into a more virulent strain and actually produce the disease it was meant to protect against. Genetic engineering would allow large-scale production of pure viral components (that is, the protein "coat" of a virus, which is how the body recognizes the virus as a foreign invader and sends out its antibodies to attack it). Such components, being only part of the virus, should be much safer while still conferring immunity. Within the past several years, researchers at MIT reported the cloning of the gene for the protein coat of polio virus and an international team announced it had used recombinant DNA technology to produce the surface antigen associated with the hepatitis

Genetic engineering is also being used by biomedical scientists who are trying to understand and control the recently identified "oncogenes" that apparently direct the wild proliferation of cells that creates a tumor. Sometimes the genetic error involved appears to be inherited; other times it apparently results from damage during a person's lifetime from chemicals, radiation, or a virus. Gene splicing may permit the genetic error to be identified early and even to be treated, although such procedures are not imminent.

D. Genetic Screening and Diagnosis

One spin-off of recombinant DNA technology exploits the specificity of restriction enzymes to help diagnose the existence of or the carrier status for a wide range of genetic disorders that until now have not been readily diagnosable.[15] The technique holds particular promise for prenatal tests and for diagnosis of late-onset disorders such as Huntington's disease. Recombinant DNA techniques allow the DNA of a gene itself to be assessed, unlike previous techniques that necessitate waiting for the gene's product (that is, an identified protein) to be manufactured.

"Restriction enzyme sites" are the specific sequences in the DNA at which one of the 150 known restriction enzymes recognizes and cuts the DNA molecule. Restriction enzymes can provide the basis for a useful assay for a particular gene in two ways: (1) if the molecular variation in the DNA of the gene is known and coincides with the cutting site for a particular restriction enzyme on the gene in question, or (2) if the restriction enzyme site lies on a variant DNA "marker" gene adjacent to the gene of interest, with which it is linked. Both techniques are

B virus.[12] Researchers are also exploring the development of vaccines for certain cancers associated with particular viruses, such as the Epstein-Barr virus and hepatitis B virus, using the antigenicity of the outer coat of the viruses.[13]

2. Cancer Diagnosis and Therapy. A major line of research in oncology today employs genetic engineering technology--in the form of cell fusion--to harness the potential power of monoclonal antibodies in the fight against cancer. Because the human body synthesizes such a huge variety of antibodies, the hope is that antibodies can be produced that are highly targeted for particular tumors and especially for the few cells that remain when a tumor is surgically excised or irradiated. Antibodies tagged with markers (such as trace amounts of radioactive chemicals) can also act like probes, permitting better diagnosis of the location and size of cancers.

Thus far, physicians have reported on only a few dozen cancer patients treated with monoclonal antibodies. The notable results of one of these early trials were announced in March 1982: a man with a rare malignancy that had defied previous treatment received a specially designed antibody and within weeks showed dramatic improvement, including the disappearance or diminution of the tumors that had proliferated throughout his body.[14] Although proof of effectiveness and an understanding of side effects must await years of clinical testing, the theory behind the technique is attractive: target a particular cell for attack by an antibody, or by a chemical poison attached to the antibody, rather than rely on current methods that involve radiation and chemicals that can have devastating effects on the body's normal cells while they attempt to destroy all the cancer cells.

based upon the fact that specific restriction enzymes cut the DNA into fragments of a characteristic length. If the sequence of the nucleotides is "abnormal" at a point that a restriction enzyme would cut, the enzyme will not cut there but at the next enzyme site, thereby producing a DNA fragment of unusual length.[16]

Mutations in the nucleotide sequence can have harmful, neutral, or beneficial consequences. Those that are deleterious put an organism at a disadvantage for survival and reproduction; hence they usually appear at very low frequencies in a population. On the other hand, some mutations persist with some frequency in a species. Occasionally, these variant forms of DNA--which are called polymorphisms--occur in the portions of the genes that actually code for proteins, apparently because they provide the organism with some survival advantage. Polymorphisms are more frequent in the introns or in the "spacer DNA" (those segments of the chromosomes that lie between the genes) because they do not code for proteins and their precise DNA sequences are thus not crucial for normal functioning.

Some genes that code for variant hemoglobins are relatively frequent, such as the gene that causes sickle-cell disease. It is an example of a mutation that, in the heterozygous form, provides a selective advantage. In regions where malaria was prevalent, people who had one gene for sickle hemoglobin (and one for normal hemoglobin) were less likely to die from malaria. In 1978, geneticists' understanding of the mutational site of the sickle-cell variant led to a direct demonstration of the primary gene mutation responsible for sickle-cell disease by using a restriction enzyme that cuts DNA at that site.[17] This procedure allowed the detection of the sickle mutation by an examination of the length of the fragments produced. Thus, sickle-cell anemia--which previously could be diagnosed prenatally only by obtaining a sample of fetal blood (a process that is more difficult and riskier than ordinary amniocentesis)--is diagnosable in fetal cells using recombinant DNA technology, although the procedure is not yet in wide clinical use.

At least in the foreseeable future, scientists do not believe that most genetic diseases will be diagnosable by finding a direct correspondence between a known mutation in the gene and a restriction site since the nature of the DNA mutation in most genetic diseases remains unknown. But two new alternative diagnostic means are now being used for a growing list of genetic conditions. The first, which depends on restriction fragment length polymorphisms, can be used even when the genetic mutation is not known. By using restriction enzymes to reveal variations in spacer DNA and in introns, scientists within a few years will have created a map of genetic landmarks on all chromosomes so that studies of genetic diseases can be undertaken to locate the genes that cause these diseases.[18] Thus, one or another DNA variant will be linked with each genetic disease. When such a "linkage" between an abnormal gene and a DNA polymorphism is used, the closer the restriction enzyme cutting site is to the gene, the more likely it is that they will be inherited together.

To apply this technique to screening, it is necessary to do studies of the genes in a family and develop the linkage patterns between the "marker" DNA and the gene of clinical interest. The finding of a specific DNA pattern in an offspring is only significant for diagnostic purposes when a parent or sibling who has the genetic condition in question has also been typed for the linked marker. Often both parents, and sometimes other relatives, have to be studied to interpret the meaning of the DNA pattern in the child.

A second new method, termed oligonucleotide hybridization, can be used when the mutation in the gene is known but does not coincide with a restriction enzyme site.[19] An assay can be performed with relatively short synthetic DNA probes that will show whether the gene or the mutant is present. The initial research has been done in a pulmonary disorder, but the first general applications are likely to be in the antenatal diagnosis of the various beta-thalassemias.

Although the diagnostic uses of gene splicing have engendered less controversy than the therapeutic uses (and, hence, receive less attention in this Report), this area of health care is one that recombinant DNA technology is likely to affect most in the immediate future. In effect, these developments will magnify the ethical considerations addressed in the Commission's report on genetic screening and counseling.[20] Genetic engineering techniques will permit the identification of a much wider range of genetic traits and conditions in utero; thus, they may greatly broaden the demand for, and even the objective of, prenatal diagnosis.

Difficult social and ethical issues will also be posed by the greatly enhanced ability of genetic screening to identify people with a susceptibility to diseases, some of which are treatable (such as colon cancer in patients with hereditary polyposis, or hemochromatosis, a disease involving a buildup of iron in the blood) and some of which are not (sucn as Huntington's disease). Genetic screening will probably be much more widely used not only in personal medical care and counseling but also in public health programs, insurance exams, and occupational or pre-employment settings as more is learned about the association between particular genotypes and disease susceptibility. Screening may permit individuals to obtain preventive medical care early or to identify those environments and behaviors that they ought to be especially careful to avoid.[21]

E. Curing Genetic Disorders

In the immediate future, the most important applications of gene splicing techniques for human health will probably be in the creation of products--hormones, enzymes, vaccines, and so forth--for human consumption and in the development of genetic screening. But in the long run, direct use of the technique in humans can be expected to have an impact that is much more significant in terms of changing people's health and developmental status, and more novel and far-reaching in conceptual and psychological terms. During 1982, the prospect of direct application of gene splicing to cure human genetic diseases moved forward by large steps, although formidable hurdles remain.

The simplest form of human gene splicing would be directed at single gene mutations, which are now known to cause more than 2000 human disorders.[22] Such a defect in just one gene--although each human cell has as many as 100,000 genes--can have tragic and even fatal consequences. Existing treatments of genetic diseases are all palliative rather than curative--that is, they are merely aimed at modifying the consequences of a defective gene. In contrast, gene splicing technology offers the possibility of correcting the defects themselves and thus curing at least some of these diseases. The effects of gene splicing might be limited to the somatic cells of the individual being treated or might, intentionally or otherwise, alter the germ cells, thereby creating a change in the genes that would be passed on to future generations.

1. Somatic Cells. The basic method proposed for using gene splicing on human beings is termed "gene therapy." This is defined as the introduction of a normal functioning gene into a cell in which its defective counterpart is active. If the mutant gene is not removed but merely supplemented, the cells may continue to produce the defective product alongside the normal product generated by the newly added gene.

Even further in the future is a theoretical possibility, sometimes referred to as "gene surgery," in which not only would the normal gene be added but the defective gene itself would either be excised or its function suppressed, so that it would no longer send out a message for a defective product in competition with the message from the inserted "normal" gene.

The technology, which researchers are now attempting to develop, involves four steps: cloning the normal gene, introducing the cloned genes in a stable fashion into appropriate target cells by means of a vector, regulating the production of the gene product, and ensuring that no harm occurs to the host cells in the patient. Only the first step--cloning a normal counterpart of a defective gene--is a straightforward matter with current knowledge and technology.

Introducing copies of the normal gene specifically to a particular set of target cells can, in theory, be achieved. Gene therapy offers the greatest promise for those single-gene defects in which an identifiable product is expressed in a discrete subpopulation of cells. For example, sickle-cell anemia and beta-thalassemia (also called Cooley's anemia) both involve alterations in the hemoglobin gene that is expressed in an accessible subpopulation of cells (that is, bone marrow cells) that could be removed from the body for gene treatment and then returned to the patient. These two diseases have therefore been among the early objects of attention for researchers designing gene therapy techniques.[23]

In most other cases, it is not practical to remove the target cells (such as brain cells in people with Tay-Sachs disease) for gene repair. A far more promising approach takes advantage of the distinctive properties of different cells, the unique markers each type of cell has on its surface. Once the unique marker for particular cells has been identified, it may be possible to construct a special "package," carrying copies of the normal gene, that will home in on this marker and deliver the new genes exclusively to the cells where the defective gene is active.

Once in the cell, the normal gene may persist as an independent unit, like a plasmid, or may integrate itself randomly somewhere in the DNA. The principal problem is inducing the host cell to produce the proper amount of the desired product.[24] Lack of expression of the normal gene would prevent the "therapy" from being effective, whereas excess production could be deleterious or even fatal. Although transposable elements of the sort that permitted new genetic material to be inserted in a nonrandom fashion and properly expressed in the experiments with fruit flies have not yet been identified in human beings, a comparable set of DNA appears to exist in human beings.

A final worry is that introducing a new gene may disrupt the functioning of the existing cells. For example, were the new piece of DNA to be spliced in the middle of another gene, it could create a gene defect that is worse than the defect the gene therapy was intended to correct.

Despite these technical stumbling blocks, two attempts have already been made at gene therapy. The first--which relied on viral transduction before recombinant DNA techniques were discovered--occurred more than a decade ago and attracted little public attention. Several German sisters had a rare metabolic error that caused them to develop a high level of a substance called arginine in their bloodstream. Left uncorrected, this genetic defect leads to metabolic and neurologic abnormalities, including severe mental retardation. No treatment for argininemia was known, so medical researchers in Germany decided to take advantage of a characteristic of the Shope virus, which, although apparently harmless to human beings, causes people exposed to it to have an unusually low level of arginine. Researchers infected the girls with the virus, in the hope that it would transfer to them its gene for the enzyme that the body needs to metabolize arginine. This attempt to add new genetic material failed--that is, the buildup of arginine continued.[25]

The second attempt at gene therapy in human beings involved a controversial experiment in 1980 on patients suffering from beta-thalassemia. A UCLA physician removed bone marrow cells from a patient in Israel and another in Italy, mixed the cells with DNA coding for hemoglobin (in the hope that a normal hemoglobin gene would be stably incorporated into the bone marrow cells), and then returned the cells to the patients. The attempt apparently neither benefited nor harmed the patients. The investigator justified the experiment on the ground of previous success in transferring foreign genes into the bone marrow of mice. The Institutional Review Board at UCLA--which must give prior approval for research involving human subjects--had refused to give permission to proceed with the experiment on the ground that more animal work was needed.[26] The experiment drew considerable criticism from other scientists, who challenged the adequacy of the animal work.[27] NIH, which had provided the principal investigator with funding, imposed sanctions, including stripping him of some of his grant funds.[28] The UCLA experiment generated considerable discussion of the ethical issues involved in gene therapy beyond the facts of that case and particularly about the appropriate time to initiate gene therapy in humans.[29]

Popular notions regarding gene therapy range from seeing it as a weapon for fighting any disease to hailing it as a tool for changing human characteristics, including removal of a hypothetical "aggression gene" from hardened criminals. These notions are unrealistic. Many diseases have multigenic or unknown etiologies; human attributes such as kindness or aggression are most certainly the result of a complex interaction of multigenic and environmental factors. The forms of genetic treatment now being discussed would be relevant to such conditions only if the effects of specific genes could be identified and particularly if some of these genes prove to be major determinants, since attempts to change a number of genes at the same time would probably be extremely difficult. It is therefore highly unlikely that in the foreseeable future predictable changes in such attributes could be achieved through genetic alterations.[30]

Gene therapy carried out on somatic cells, such as bone marrow cells, would resemble standard medical therapies in that they all involve changes limited to the cells of the person being treated. They differ, however, in that gene therapy involves an inherent and probably permanent change in the body rather than requiring repeated applications of an outside force or substance. An analogy is organ transplantation, which also involves the incorporation into an individual of cells containing DNA of "foreign" origin.

2. Germ-Line Cells. Thus far, attempts at gene therapy have focused on treating a discrete population of patients' somatic cells. Some researchers believe that certain forms of gene therapy that have been considered, such as the use of a virus to carry the desired gene to the patient's cells, might also affect germinal cells. Furthermore, gene therapy could also be applied to fertilized human eggs (zygotes) in conjunction with in vitro fertilization techniques.[31] Whereas the effects of genetic therapy on somatic cells would be expected to be limited to the individual patient treated, DNA therapy of fertilized eggs would probably affect all cells--including the germ cells--of the developing embryo; assuming normal birth, development, and reproduction, the individual would then pass on the altered gene to his or her offspring according to Mendelian rules. Zygote therapy would thus involve an alteration of the genetic inheritance of future generations and a significant departure from standard medical therapy.

To date, genetic engineering experiments using zygotes have been conducted for academic rather than therapeutic reasons. Several laboratories are currently working on fertilized mouse eggs. In one experiment, mice developed from zygotes injected with the rabbit hemoglobin gene were reported to contain rabbit hemoglobin in their red blood cells.[32] The medical significance is obvious. In a case where both parents are carriers of a particular recessive disorder the risk of an affected child is one in four. But if the relevant normal gene could safely be introduced in vitro to a fertilized egg of that couple, the individual who resulted from the egg would not have the disease and none of his or her descendants would be at risk of that disease.

Zygote therapy differs significantly from gene therapy on somatic cells in several ways. First, from the standpoint of the individual it may be useful in the treatment of genetic diseases, like cystic fibrosis, that affect many tissues--lungs, pancreas, intestines, and sex organs--rather than a discrete, accessible subpopulation of cells. Successful treatment at a very early stage of development would confer "good" genes to all the organs of an afflicted individual. Second, from the societal standpoint, such therapy if ever practiced on a vast scale could potentially reduce the overall frequency in the population of genes that usually have deleterious consequences, such as the sickle-cell gene.

Although zygote therapy may hold great promise, it is also fraught with technical risks and uncertainties. First of all, the technique itself is largely unproven, even with laboratory animals. For example, the success rate of microinjecting genes into mouse embryos remains low. Increasing the amount of DNA injected into a zygote makes it more likely that a gene will be incorporated, but it also increases the mortality rate of embryos. Microinjection of DNA into zygotes is obviously not a benign procedure.

The second major technical drawback at present is that transferred genes integrate randomly in the genome. Depending on the site of integration and perhaps the physiological state of the embryo, some of the foreign genes may be expressed and others not. Thus far, in experiments with mice, genes are rarely expressed in a tissue-specific way.[33] Even then, expression of the microinjected foreign gene in somatic tissue has not resulted in stable inheritance of that expression,[34] which is essential if the purpose is to introduce a new trait permanently. The consequences of having the wrong tissues producing the products of inserted genes could be disastrous.[35]

Finally, as in gene therapy on somatic cells, introducing foreign DNA into the zygote may affect the regulation of the cell in some undetermined way. Embryological development depends on a precise set of genetic instructions; disruption of this process is therefore much more likely to have serious adverse consequences than a disruption of the regulatory mechanisms operating in a subset of somatic cells. Instead of being therapeutic, therapy on zygotes or on more-developed embryos might be teratogenic and increase the incidence of congenital abnormalities.

In addition to the technical uncertainties involved, genetic manipulation of embryos raises serious ethical concerns. Altering the human gene pool by eliminating "bad" traits is a form of eugenics, about which there is strong concern. In 1982, the Council of Europe requested "explicit recognition in the European Human Rights Convention of the right to a genetic inheritance which has not been interfered with, except in accordance with certain principles which are recognized as being fully compatible with respect for human rights."[36]

Yet the meaning of "respect for human rights" is vague. Some favor gene therapy in embryos because it offers a treatment other than abortion for genetic defects. But--especially in the early years while techniques are being perfected--it would probably be standard practice to examine the genetic and cytologic "health" of any embryos and either not to implant or, if already implanted, to abort any found to be abnormal.

Not to do so would risk creating offspring who have genetic problems created by the "therapy" rather than naturally occurring defects.[37]

Furthermore, unless the presence or absence of a genetic defect could be established at a very early stage without harm--that is, at or just prior to fertilization or in a 2 to 4 cell zygote--it would be difficult to determine to whom gene therapy ought to be applied. Yet without such a determination, the use of gene splicing as a "treatment" seems dubious. In most cases identified by genetic screening, both parents are carriers of a recessive condition (those who have only a single defective gene of a pair and do not manifest the disease); in such cases, there is only a 25% chance that any embryo has the disease. It would not seem appropriate to run the risk of zygote therapy when three out of four of the potential "patients" do not need treatment.

Therefore, the technical uncertainties, the ethical implications, and the low probability of actually treating an affected person are strong contraindications against therapy of fertilized eggs or embryos becoming a useful clinical option in the near future.

F. Genes or Genies?

Biotechnology has made rapid advances in the past decade and will most likely continue to be a rapidly unfolding field. The awesome power entailed in these developments can be likened to the genie being let out of the bottle. As one observer of the field has noted:

> Some thirty-five years ago physicists learned how to manipulate the forces in the nucleus of the atom, and the world has been struggling to cope with the results of that discovery ever since. The ability to penetrate the nucleus of the living cell, to rearrange and transplant the nucleic acids that constitute the genetic material

> of all forms of life, seems a more beneficient power but one that is likely to prove at least as profound in its consequences.[38]

Stopping any enterprise out of a fear of potential evil not only deprives humanity of the fruits of new findings but also stifles strong impulses for innovation and change. Nevertheless, the technological allure of gene splicing ought not to be allowed to blind society to the need for sober judgments, publicly arrived at, about whether there are instances in which the price of going ahead with an experiment or an innovation will be higher than that paid by stopping the work.[39] In the next two chapters, the Commission examines the issues raised by gene splicing--particularly when used in human therapy—and the mechanisms for monitoring this field.

FOOTNOTES

1. For a history of developments in biochemical and molecular genetics, see Horace Freeland Judson, *The Eighth Day of Creation*, Simon and Schuster, New York, N.Y. (1979).

2.
> Thus, the underlying issue in the recombinant DNA research debate is the accommodation of knowledge-thrust and the public interest. Shall unfolding knowledge determine our desired future or shall our hoped-for future contribute to choices regarding the direction of knowledge-thrust?

Clifford Grobstein, *Regulation and Basic Research: Implications of Recombinant DNA*, 51 S. Cal. L. Rev. 1181, 1199 (1978).

3. Lymphocytes, the cells that produce antibodies (proteins that protect vertebrates from harm by foreign invaders such as viruses and bacteria), engage in a form of natural recombination whereby the DNA segments needed to construct antibody genes combine in many different ways. Therefore, each clone of lymphocyte cells, which protects against a different invader, has a somewhat different configuration of genes than the other cells in the organism. *See* Maxine Singer, *The Genetic Program of Complex Organisms*, in 3 The Outlook for Science and Technology: The Next Five Years, National Academy Press, Washington (1982) at 1, 24-25.

4. The four letters are from the name of the base in the nucleotide: A (adenine), G (guanine), T (thymine), and C (cytosine).

5. Raoul E. Benveniste and George J. Todaro, *Gene Transfer Between Eukaryotes*, 217 Science 1202 (1982).

6. In higher organisms that reproduce sexually, a high degree of genetic variation is produced by the normal process of crossing-over of genes in the germ cells. Crossing-over, like the other processes, involves the formation of new combinations of genes.

7. These enzymes, which make it possible to cut DNA at predetermined places, exist as part of the defense system that bacteria use to respond to foreign DNA (from a virus, for example). Restriction enzymes cut the DNA of the invader into small pieces, while another substance protects the bacteria's own DNA from getting chopped up.

8. Gerald M. Rubin and Allan C. Spradling, *Genetic Transformation of Drosophilia Germ Line Chromosomes*, 218 Science 348 (1982).

9. Diamond v. Chakrabarty, 447 U.S. 303 (1980).

10. Lawrence K. Altman, *U.S. Unit Backs Human Insulin for the Market*, N. Y. Times, Oct. 30, 1982, at A-1.

11. Marjorie Sun, *Interferon: No Magic Bullet Against Cancer*, 212 Science 141 (1981); Michael Edelhart, *Putting Interferon to the Test*, N. Y. Times, April 26, 1981 (Magazine), at 30.

12. V. R. Racaniello and D. Baltimore, Cloned Poliovirus Complementary DNA is Infectious in Mammalian Cells, 20 Science 916 (1981); P. Charnay et al. Biosynthesis of Hepatitis B. Virus Surface Antigen in Escherichia Coli., 286 Nature 893 (1980).

13. Baruch S. Blumberg et al., The Relation of Infection With the Hepatitis B Agent to Primary Hepatic Carcinoma, 81 Am. J. Psthology 669 (1975); Mark Pasek et al., Hepatitis B Virus Genes and Their Expression in E-Coli, 282 Nature 575 (1979). The production of vaccines for diseases affecting domestic animals is also being very actively pursued. Other agricultural uses (engineering new traits in plants and animals rather than breeding for these traits), as well as industrial and mining uses of gene splicing, are being vigorously explored in academic and commercial laboratories in this country and elsewhere. Office of Technology Assessment, Impacts of Applied Genetics--Micro-Organisms, Plants, and Animals, U.S. Congress, U.S. Government Printing Office, Washington (1981).

14. Richard A. Miller et al., Treatment of B-Cell Lymphoma with Monoclonal Anti-Idiotype Antibody, 306 New Eng. J. Med. 517 (1982).

15. See, e.g., Alan E. Emery, Recombinant DNA Technology, 2 Lancet 1406 (1981).

16. Arlene Wyman and R.L. White, Restriction Fragment Length Polymorphism in Human DNA, 77 Proc. Nat'l. Acad. Sci. 6754 (1980); D. Botstein et al., Construction of a Genetic Linkage Map in Man Using Restriction Fragment Length Polymorphisms, 32 Am. J. Human Genetics 314 (1980).

17. Y.W. Kan and A. M. Dozy, Antenatal Diagnosis of Sickle-Cell Anemia by DNA Analysis of Amniotic-Fluid Cells, 2 Lancet 910 (1978).

18. David T. Bishop et al., The Number of Polymorphic DNA Clones Required to Map the Human Genome, in Bruce Weir, ed., Statistical Analysis of DNA Sequence Data (in press); Mark H. Skolnick and U. Francke, Report of the Committee on Human Gene Mapping by Recombinant DNA Techniques, 32 Cytogenetics & Cell Genetics 194 (1982).

19. Savio Woo et al., Alpha-1 Antitrypsin Deficiency and Pulmonary Emphysema: Identification of Recessive Homozygote by Direct Analysis of the Mutation Site in the Chromosomal Genes (Cold Spring Harbor Symposium on the Application of Recombinant DNA to Human Disease, 1982; in press).

20. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, Screening and Counseling for Genetic Conditions, U. S. Government Printing Office, Washington (1982).

21. Eventually, medical scientists may be able to identify not only restriction enzyme sites that are tightly linked to known gene defects and some that are actually located at the exact site of a mutation, but also the presence or absence of genes that are responsible for other human characteristics, even those that would not be detectable through looking for their biochemical "footprints," as is now done, for example, in measuring the level of serum phenylalinine in screening

for phenylketonuria (PKU). Of course, most interesting human characteristics are believed to result from the interaction of the environment with a number of genes, rather than a single gene, which would make "screening" an exceedingly complex task.

22. Victor A. McKusick, Mendelian Inheritance in Man, Johns Hopkins Univ. Press, Baltimore (6th ed. 1982).

23. Richard Roblin, *Human Genetic Therapy: Outlook and Apprehensions*, in George K. Chacko, ed., Health Handbook, North Holland Pub. Co., Amsterdam (1979) at 103, 108-12.

24. Jean L. Marx, *Still More About Gene Transfer*, 218 Science 459 (1982).

25. W. French Anderson, *Genetic Therapy*, in Michael P. Hamilton, ed., The New Genetics and the Future of Man, William B. Eerdmans Pub. Co., Grand Rapids, Mich. (1972) at 109, 118.

26. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, Protecting Human Subjects, U.S. Government Printing Office, Washington (1981) at 177, 182.

27. In the opinion of Dr. Bob Williamson, a molecular geneticist at the University of London:

> Cline's experiments were *fundamentally* unethical. His own work on mice shows that there was no basis for hope that globin gene insertion into marrow cells could give clinical benefit at that time. [The subjects'] families were given hope that the gene therapy might help them in their fight for survival. It is unacceptable that patients should be misled in this way.

Bob Williamson, *Gene Therapy*, 298 Nature 416, 418 (1982). *See also*, Nicholas Wade, *UCLA Gene Therapy Racked by Friendly Fire*, 210 Science 509 (1980).

28. Marjorie Sun, *Cline Loses Two NIH Grants*, 214 Science 1220 (1981).

29. An ethicist and a scientist at the National Institutes of Health suggest that three conditions should be met in animal studies before it is ethical to initiate trials of human gene therapy: (1) the new gene should be put into target cells and remain in them; (2) the new gene should be regulated appropriately; and (3) the presence of the new gene should not harm the cell. W. French Anderson and John C. Fletcher, *Gene Therapy in Human Beings: When is it Ethical to Begin?*, 303 New Eng. J. Med. 1293 (1980). *See also*, Arno G. Motulsky, *Impact of Genetic Manipulation on Society and Medicine*, Science (in press).

30. Williamson, *supra* note 27.

31. The approach would involve the following: (1) isolating and amplifying the desired gene by standard recombinant DNA techniques, (2) removing a mature ovum from a woman and fertilizing it *in vitro*, (3) injecting copies of the cloned gene into the fertilized egg (zygote) using microsurgical techniques, and (4) implanting the genetically altered zygote into the woman's uterus.

32. Thomas E. Wagner *et al.*, *Microinjection of a Rabbit B-globin Gene into Zygotes and Its Subsequent Expression in Adult Mice and Their Off-Spring*, 78 Proc. Nat'l. Acad. Sci. 6376 (1981).

33. Ralph L. Brinster *et al.*, *Somatic Expression of Herpes Thymidine Kinase in Mice Following Injection of a Fusion Gene into Eggs*, 27 Cell 223 (1981).

34. Richard D. Palmiter *et al.*, *Differential Regulation of Metallothionein--Thymidine Kinase Fusion Genes in Transgenic Mice and Their Offspring*, 29 Cell 701 (1982).

35. Bob Williamson, *Reintroduction of Genetically Transformed Bone Marrow Cells into Mice*, 284 Nature 397 (1980).

36. Council of Europe Parliamentary Assembly, 23rd Ordinary Session, *Recommendation 934*, Strasbourg (1982).

37. Paul Ramsey, Fabricated Man, Yale University Press, New Haven, Conn. (1970) at 75-97.

38. Nicholas Wade, The Ultimate Experiment, Walker and Company, New York (1977) at 2.

39. As Chief Justice Burger observed, some of the arguments presented against issuance of a patent for the oil-eating bacteria "remind us that, at times, human ingenuity seems unable to control fully the forces it creates--that with Hamlet, it is sometimes better 'to bear those ills we have than fly to others that we know not of.'" Diamond v. Chakrabarty, 447 U.S. 303, 316 (1980).

CHAPTER 3: SOCIAL AND ETHICAL ISSUES

The preceding chapters have described the potential benefits of gene splicing, but they have also suggested the awesome and sometimes troubling implications that have shared this technology's spotlight. In this chapter, the Commission considers the social and ethical issues raised as society seeks ways to realize the benefits without incurring unacceptable risks. The Commission has found no ethical precepts that would preclude the initial clinical uses of gene splicing now being undertaken or planned or that would categorically prohibit the research procedures through which knowledge is currently being sought in this important field. But more distant possibilities--either in themselves or in conjunction with other scientific and social developments they may foster--could have less benign effects. Consequently, this Report recommends steps that can and should be taken to keep the social and ethical implications of gene splicing before the public and policymakers as these developments become feasible in the years ahead.

The Commission also believes, for several reasons, that balancing both present and future benefits and risks requires more than a simple arithmetical calculation. First, assessing this new technology through cost/benefit or risk/benefit analysis is complex because decisionmaking about gene splicing technology is characterized by several types and levels of uncertainty. The risks and benefits are poorly conceptualized and understood. Before they can be compared, they must be more clearly distinguished and articulated. Moreover, in many cases consensus--social or scientific--is lacking about whether a particular outcome is in fact a benefit or a detriment. For example, some people regard the prospect of eliminating a genetic disorder in future generations as laudable, while others worry about the unforeseeable consequences of making alterations in germ-line cells. Second, while some people focus on particular consequences of various applications of genetic engineering technology, others are concerned about the acceptability of genetic manipulation per se. In this context, balancing risks against benefits makes little sense because actions, not consequences, are at issue.

In the first part of this chapter, the Commission considers theological and secular attitudes toward the technology as such, rather than toward its possible consequences, and attempts to clarify the nature of these concerns. The Commission then turns to an examination of the types of risks at issue. Although the focus is on spelling out the meaning and significance of certain risks, the benefits being sought through genetic manipulations--and those foregone if progress is thwarted--are also part of the equation.

It should be emphasized that this discussion does not limit itself to concerns about gene splicing that the scientific community or the Commissioners view as valid. Moreover, this chapter is not a comprehensive survey of the social and ethical issues in genetic engineering. Since this Report addresses primarily the potential human uses of gene splicing, there is, for example, no detailed treatment of the subject of laboratory or industrial "biohazards" (that is, the danger of microorganisms to those involved in their creation or manufacture, or to the general public should they escape from a controlled environment). The problems of laboratory hazards and occupational safety have been scrutinized for almost a decade by the United States Congress (through hearings and through studies by the Office of Technology Assessment and the Library of Congress), by RAC, by various bodies at the Federal, state, and local level, and by numerous scientific organizations.[1]

Some of the doubts about the new technology may appear on close examination to be overly speculative or even fanciful. Nonetheless, they have been forcefully expressed in the popular press, by religious writers, and by members of the general public, and they represent important concerns about the responsible exercise of what may prove to be the means by which people achieve freedom from some of the dictates of their genetic inheritance.

The Commission believes it is important for society to address these concerns head-on. If some of these fears prove groundless, the clearing away of spurious issues will make it easier to focus on any problems of real concern. Without necessarily resolving the problems, the Commission tries to go beyond clarification of the issues to recommend concrete steps for dealing with them.

A. Concerns About "Playing God"

Hardly a popular article has been written about the social and ethical implications of genetic engineering that does not suggest a link between "God-like powers" and the ability to manipulate the basic material of life. Indeed, a popular book about gene splicing is entitled _Who Should Play God?_[2], and in their June 1980 letter to the President, the three religious leaders sounded a tocsin against the lack of a governmental policy concerning "[t]hose who would play God" through genetic engineering.[3]

1. _Religious Viewpoints_. The Commission asked the General Secretaries of the three religious organizations to elaborate on any uniquely theological considerations underlying their concern about gene splicing

in humans. The scholars appointed by the organizations to address this question were asked to draw specifically on their particular religious tradition to explain the basis of concerns about genetic engineering; further commentary was provided by other religious scholars.[4]

In the view of the theologians, contemporary developments in molecular biology raise issues of responsibility rather than being matters to be prohibited because they usurp powers that human beings should not possess. The Biblical religions teach that human beings are, in some senses, co-creators with the Supreme Creator.[5] Thus, as interpreted for the Commission by their representatives, these major religious faiths respect and encourage the enhancement of knowledge about nature, as well as responsible use of that knowledge.[6] Endorsement of genetic engineering, which is praised for its potential to improve the human estate, is linked with the recognition that the misuse of human freedom creates evil and that human knowledge and power can result in harm.

While religious leaders present theological bases for their concerns, essentially the same concerns have been raised--sometimes in slightly different words--by many thoughtful secular observers of contemporary science and technology. Concerns over unintended effects, over the morality of genetic manipulation in all its forms, and over the social and political consequences of new technologies are shared by religious and secular commentators. The examination of the various specific concerns need not be limited, therefore, to the religious format in which some of the issues have been raised.

2. Fully Understanding the Machinery of Life. Although it does not have a specific religious meaning, the objection to scientists

"playing God" is assumed to be self-explanatory. On closer examination, however, it appears to the Commission that it conveys several rather different ideas, some describing the power of gene splicing itself and some relating merely to its consequences.

At its heart, the term represents a reaction to the realization that human beings are on the threshold of understanding how the fundamental machinery of life works.[7] A full understanding of what are now great mysteries, and the powers inherent in that understanding, would be so awesome as to justify the description "God-like." In this view, playing God is not actually an objection to the research but an expression of a sense of awe--and concern.

Since the Enlightenment, Western societies have exalted the search for greater knowledge, while recognizing its awesome implications. Some scientific discoveries reverberate with particular force because they not only open new avenues of research but also challenge people's entire understanding of the world and their place in it. Current discoveries in gene splicing--like the new knowledge associated with Copernicus and Darwin--further dethrone human beings as the unique center of the universe. By identifying DNA and learning how to manipulate it, science seems to have reduced people to a set of malleable molecules that can be interchanged with those of species that people regard as inferior. Yet unlike the earlier revolutionary discoveries, those in molecular biology are not merely descriptions; they give scientists vast powers for action.

3. Arrogant Interference with Nature. By what standards are people to guide the exercise of this awesome new freedom if they want to act

responsibly? In this context, the charge that human beings are playing God can mean that in "creating new life forms" scientists are abusing their learning by interfering with nature.

But in one sense all human activity that produces changes that otherwise would not have occurred interferes with nature. Medical activities as routine as the prescription of eyeglasses for myopia or as dramatic as the repair or replacement of a damaged heart are in this sense "unnatural." In another sense, human activity cannot interfere with nature--in the sense of contravening it--since all human activities, including gene splicing, proceed according to the scientific laws that describe natural processes. Ironically, to believe that "playing God" in this sense is even possible would itself be hubris according to some religious thought, which maintains that only God can interfere with the descriptive laws of nature (that is, perform miracles).

If, instead, what is meant is that gene splicing technology interferes with nature in the sense that it violates God's prescriptive natural law or goes against God's purposes as they are manifested in the natural order, then some reason must be given for this judgment. None of the scholars appointed to report their views by the three religious bodies that urged the Commission to undertake this study suggested that either natural reason or revelation imply that gene splicing technology as such is "unnatural" in this prescriptive sense. Although each scholar expressed concern over particular applications of gene splicing technology, they all also emphasized that human beings have not merely the right but the duty to employ their God-given powers to harness nature for human benefit. To turn away from gene splicing, which may provide a means of curing hereditary diseases, would itself raise serious ethical problems.[8]

4. Creating New Life Forms. If "creating new life forms" is simply producing organisms with novel characteristics, then human beings create new life forms frequently and have done so since they first learned to cultivate new characteristics in plants and breed new traits in animals. Presumably the idea is that gene splicing creates new life forms, rather than merely modifying old ones, because it "breaches species barriers" by combining DNA from different species--groups of organisms that cannot mate to produce fertile offspring.

Genetic engineering is not the first exercise of humanity's ability to create new life forms through nonsexual reproduction. The creation of hybrid plants through grafting seems no more or no less natural than the development of a new strain of E. coli bacteria through gene splicing. Further, genetic engineering cannot accurately be called unique in that it involves the creation of new life forms through processes that do not occur in nature without human intervention. As described in Chapter Two, scientists have found that the transfer of DNA between organisms of different species occurs in nature without human intervention. Yet, as one eminent scientist in the field has pointed out, it would be unwarranted to assume that a dramatic increase in the frequency of such transfers through human intervention is not problematic simply because DNA transfer sometimes occurs naturally.[9]

In the absence of specific religious prohibitions, either revealed or derived by rational argument from religious premises, it is difficult to see why "breaching species barriers" as such is irreligious or otherwise objectionable. In fact, the very notion that there are barriers that must be breached prejudges the issue. The question is simply whether there is something intrinsically wrong with intentionally crossing species lines. Once the question is posed in this way the answer must be negative--unless one is willing to condemn the production of tangelos by hybridizing tangerines and grapefruits or the production of mules by the mating of asses with horses.

There may nonetheless be two distinct sources of concern about crossing species lines that deserve serious consideration. First, gene splicing affords the possibility of creating hybrids that can reproduce themselves (unlike mules, which are sterile). the possibility of self-perpetuating "mistakes" adds a new dimension of concern, although here again, the point is not that crossing species lines is inherently wrong, but that it may have undesirable consequences and that these consequences may multiply beyond human control. As noted, the Commission's focus on the human applications of gene splicing has meant that it does not here address this important set of concerns, which lay behind the original self-imposed moratorium on certain categories of gene splicing research and which have been, and continue to be, addressed through various scientific and public mechanisms, such as RAC.[10]

Second, there is the issue of whether particular crossings of species--especially the mixing of human and nonhuman genes--might not be illicit. The moral revulsion at the creation of human-animal hybrids may be traced in part to the prohibition against sexual relations between human beings and lower animals. Sexual relations with lower animals are thought to degrade human beings and insult their God-given dignity as the highest of God's creatures. But unease at the prospect of human-animal hybrids goes beyond sexual prohibitions.

The possibility of creating such hybrids calls into question basic assumptions about the relationship of human beings to other living things. For example, those who believe that the current treatment of animals—in experimentation, food production, and sport—is morally suspect would not be alone in being troubled by the prospect of exploitive or insensitive treatment of creatures that possess even more human-like qualities than chimpanzees or porpoises do. Could genetic engineering be used to develop a group of virtual slaves—partly human, partly lower animal—to do people's bidding? Paradoxically, the very characteristics that would make such creatures more valuable than any existing animals (that is, their heightened cognitive powers and sensibilities) would also make the moral propriety of their subservient role more problematic. Dispassionate appraisal of the long history of gratuitous destruction and suffering that humanity has visited upon the other inhabitants of the earth indicates that such concerns should not be dismissed as fanciful.

Accordingly, the objection to the creation of new life forms by crossing species lines (whether through gene splicing or otherwise) reflects the concern that human beings lack the God-like knowledge and wisdom required for the exercise of these God-like powers. Specifically, people worry that interspecific hybrids that are partially human in their genetic makeup will be like Dr. Frankenstein's monster. A striking lesson of the Frankenstein story is the uncontrollability and uncertainty of the consequences of human interferences with the natural order. Like the tale of the Sorcerer's apprentice or the myth of the golem created from lifeless dust by the 16th century rabbi, Loew of Prague, the story of Dr. Frankenstein's monster serves as a reminder of the difficulty of restoring order if a creation intended to be helpful proves harmful instead. Indeed, each of these tales conveys a painful irony: in seeking to extend their control over the world, people may lessen it. The artifices they create to do their bidding may rebound destructively against them--the slave may become the master.

Suggesting that someone lacks sufficient knowledge or wisdom to engage in an activity the person knows how to perform thus means that the individual has insufficient knowledge of the consequences of that activity or insufficient wisdom to cope with those consequences. But if this is the rational kernel of the admonition against playing God, then the use of gene splicing technology is not claimed to be wrong as such but wrong because of its potential consequences. Understood in this way, the slogan that crossing species barriers is playing God does not end the debate, but it does make a point of fundamental importance.[11] It emphasizes that any realistic assessment of the potential consequences of the new technology must be founded upon a sober recognition of human fallibility and ignorance. At bottom, the warning not to play God is closely related to the Socratic injunction "know thyself": in this case, acknowledge the limits of understanding and prediction, rather than assuming that people can foresee all the consequences of their actions or plan adequately for every eventuality.[12]

Any further examination of the notion that the hybridization of species, at least when one of the species is human, is intrinsically wrong (and not merely wrong as a consequence of what is done with the hybrids) involves elaboration of two points. First, what characteristics are uniquely human, setting humanity apart from all other species? And second, does the wrong lie in bestowing some but not all of these characteristics on the new creation or does it stem from depriving the being that might otherwise have arisen from the human genetic material of the opportunity to have a totally human makeup? The Commission believes that these are important issues deserving of serious study.

It should be kept in mind, however, that the information available to the Commission suggests that the ability to create interspecific hybrids of the sort that would present intrinsic moral and religious concerns will not be available in the foreseeable future. The research currently being done on experimentation with recombinant DNA techniques through the use of single human genes (for example, the insertion of a particular human hemoglobin gene into mouse cells at the embryonic stage) or the study of cellular development through the combining of human genetic material with that of other species in a way that does not result in a mature organism (for example, _in vitro_ fusion of human and mouse cells) does not, in the Commission's view, raise problems of an improper "breaching of the barriers."

B. Concerns About Consequences

To appreciate the complexity of the problem of assessing potential consequences and the individual and societal ability to cope with them, the several types of uncertainty discussed in Chapter One must be considered: the occurrence uncertainty that arises when it is not known whether a particular event will take place (or what sort of future it will take place in), the ethical uncertainty that follows from not knowing whether certain uses of a technology should be regarded as beneficial or harmful, and the conceptual uncertainty that attends new developments that challenge people's fundamental beliefs. The presence of any of these types of uncertainty complicates the task of estimating whether the potential benefits of genetic engineering outweigh the potential risks.

1. What Are the Likely Outcomes?

a. Medical applications. Two broad applications may be distinguished: the use of drugs produced by gene splicing (such as interferon or insulin) and the direct application of gene splicing to human beings through gene therapy or gene surgery.

The problems of personal safety involved in using drugs produced by gene splicing techniques do not appear to be radically different from those that accompany conventionally produced drugs. The basic scientific and ethical issues in this broad area are well known and need not be rehearsed here. The appropriate divisions within the Department of Health and Human Services (in particular, the relevant institutes of the NIH and the Office for Protection from Research Risks, regarding Federally supported research, and the Food and Drug Administration, regarding all drug and vaccine research) need to consider how to apply to genetically engineered drugs the existing mechanisms related to the margin of acceptable risk, the extent and type of animal and human studies required, the standards for manufacturers, and the decision to allow seriously ill patients to opt for more dangerous or less well tested experimental drugs.[13] According to the Department, appropriate steps are already being taken, especially by FDA, to resolve these issues, and the first product of gene splicing has already been approved.[14]

Some direct therapeutic applications of gene splicing technologies to human beings may present distinctive problems of uncertainty not ordinarily encountered in more conventional medical practice. Concern has been expressed that serious harm might result, for example, from a malfunctioning gene inserted by gene therapy. Yet even here the ethical and policy issues do not seem appreciably different from those involved in the development of any new diagnostic and therapeutic techniques. However, in the case of genetic interventions that involve alteration of germ cells, especially stringent animal testing and other precautions are appropriate, since any physicial harms produced might extend to the subject's progeny.

Most experts agree there is a very small likelihood that inheritable changes in germ cells would inadvertently occur when the genetic material of somatic cells is being manipulated. However, the same animal tests and refinements of theoretical models that should precede the use of gene surgery in human beings may shed further light on whether such changes might produce inheritable changes in characteristic functions and whether they will influence germ cells. In both cases, the resolution of uncertainty depends upon increased understanding of how an inserted gene will perform its function.

Subjects of gene therapy or gene surgery might suffer psychological as well as physical harm. The revelation that a person has a genetic defect or is genetically predisposed to a disease may produce anxiety, fear, or loss of self-esteem--feelings that may be intensified by the belief that the defect is a part of a person's constitution, rather than an outside influence. Similarly, patients might regard alterations of their genes as a more profound change than a surgical procedure or the ingestion of a drug. Experience with genetic screening and counseling suggests that the special significance of a genetic condition to the individual may be accompanied by social stigma based on ignorance, but that efforts to educate individual patients and their families as well as the general public can minimize this problem.[15]

b. Evolutionary impact on human beings. Some critics warn against the dangers of attempting to control or interfere with the "wisdom of evolution" in order to satisfy scientific curiosity.[16] Those who hold this view object in particular to crossing species lines by gene splicing because they believe that the pervasive inability of different species to produce fertile offspring by sexual reproduction must be an adapative feature, that is, it must confer some significant survival advantage. Thus they view species lines as natural protective barriers that human beings may circumvent only at their peril, although the harm such barriers are supposed to shield people from remains unspecified.

Most proponents of genetic engineering argue that the benefits it will bring are more tangible and important and will affect more people than those objecting suggest. Further, the notion of the "wisdom of evolution" that apparently underlies this consequentialist version of the objection to crossing species lines is not well founded. As the scientific theory of evolution does not postulate a plan that the process of evolution is to achieve, evolutionary changes cannot be said to promote such a plan, wisely or unwisely. Moreover, evolutionary theory recognizes (and natural history confirms) that a "wise" adaptation at one time or place can become a lethal flaw when circumstances change. So even if it could be shown that species barriers have thus far played an important adaptive role, it would not follow that this will continue. An evolutionary explanation of any inherited characteristic can at most show that having that characteristic gave an organism's ancestors some advantage in enabling them to live long enough to reproduce and that the characteristic has not yet proved maladaptive for the offspring.

Furthermore, as a philosopher concerned with assessing the risks of genetic engineering has recently noted, the ability to manipulate genes, both within and across species lines, may become a crucial asset for survival.

> There may...come a time when, because of natural or man-induced climatic change, the capacity to alter quickly the genetic composition of agricultural plants will be required to forestall catastrophic famine.[17]

The consequentialist version of the warning against crossing species lines seems, then, to be no more a conclusive argument against genetic engineering than the admonition that to cross species lines is wrong because it is playing God. But it does serve the vital purpose of urging that, so far as this is possible, the evolutionary effects of any interventions are taken into account.

One effect that is of particular concern to some observers is the loss of "heterozygote advantage"--the strength (in terms of individual health and species survival) engendered when members of a species have a variety of gene variants rather than all having the same gene. This advantage has two aspects. The first is the protection that varied genes offer for survival of a species in case of a radical change in environment or, more particularly, the occurrence of a novel pathogen. Of course, it would be virtually impossible to know which particular, rare gene variant would prove to be valuable under such circumstances. This consideration would favor preserving as much genetic variation as possible, but it would be difficult to weigh this against the benefit to offspring of the variant gene in its homozygous form.

The second aspect is the advantage that may be conferred by a particular gene in past (and present) environments, perhaps accounting for its prevalence in a population. Although the existence of such an advantage could be construed as an argument against making inheritable gene changes, very little is actually known about the existence and nature of such advantages for most genes. The only instance that is widely acknowledged is the advantage, in terms of longevity and reproduction, possessed by sickle-cell carriers in tropical regions where malaria has been endemic.[18]

The possible beneficial effects of most gene variants are typically too small to be detected by current research methods--that is, other genetic and environmental effects on the health, longevity, and reproductive history of a population make it difficult to detect whether a particular gene confers any advantage on those who possess it. If it becomes feasible to remove an apparently deleterious gene from a population through routine use of gene surgery, the possible loss of heterozygote advantage will deserve careful evaluation.[19] Population geneticists tend to regard the loss of even minute advantages as serious, since such advantages can confer marked benefits on a species over a great many generations. Medical geneticists, on the other hand, are much less bothered by such losses because they believe that it should be possible to make up, through environmental manipulation (including medical treatment) for the loss of any advantage provided by a variant in any probable future environment.

2. Will Benefit or Harm Occur?

a. Parental rights and responsibilities. Current attitudes toward human reproductive activity are founded, in part, on several important assumptions, among them that becoming a parent requires a willingness, within very broad limits, to accept the child a woman gives birth to, that parents' basic duties to children are more or less clear and settled, and that reproduction and parenting are and should remain largely private and autonomous spheres of people's lives. The doors that genetic engineering can open challenge all three of these assumptions.

Genetic counseling and screening have already undercut the first assumption by enabling parents to make an informed decision to prevent the occurrence of some genetic defects by terminating pregnancy, by artificial insemination, or by avoiding conception. If gene therapy or gene surgery become available, parents could have more control over their children's characteristics. They will no longer face the stark alternatives of either playing the hand their child has been dealt by the "natural lottery" or avoiding birth or conception. Instead, they could prevent some genetic defects through gene surgery on the embryo and remedy others through gene therapy before the genetic defect produces irreversible changes in the child.

With this increased ability to act for the well-being of the child would come an expansion of parental responsibility. The boundaries of this responsibility--and hence people's conception of what it is to be a good parent--may continue to shift rapidly. It seems safe to say that the most important duty of a parent is to prevent or ameliorate serious defects (if it can be done safely) and that the duty to enhance favorable characteristics is less stringent and clear. Yet the new technological capabilities may change people's view of what counts as a defect. For example, if what is now regarded as the normal development of important cognitive skills could be significantly augmented by genetic engineering, then today's "normal" level might be considered deficient tomorrow. Thus ethical uncertainty about the scope of a parent's obligation is linked to conceptual uncertainty about what counts as a defect.

The problem of shifting conceptions of parental responsibility becomes even more complicated when the effects of parents' present actions on descendants beyond their immediate offspring are considered. Deciding whether to engineer a profound change in an expected or newborn child is difficult enough; if the change is inheritable, the burden of responsibility could be truly awesome.

Gene splicing technology may also change people's sense of family and kinship. On the one hand, the possibility of promoting significant inheritable changes through gene surgery may encourage people to think of their family as extending further into the future than they now do. On the other hand, knowing that future generations may employ an even more advanced technology to alter or replace the characteristics passed on to them may weaken people's sense of genetic continuity.

Traditional views of family and kinship associate reproduction with genetic contribution. If genetic engineering makes use of reproductive technologies such as artificial insemination and in vitro fertilization, it will increase the strains on this concept of lineage. Whether or not they are accurate, people's beliefs that they are linked to other members of their family by constitutional similarities may play an important role in a family's sense of solidarity and group identity. Knowledge that the genetic link between parents and children is only partial or nonexistent could attenuate these feelings of kinship and family and the sense of continuity and support that they foster. Experience with adoption illustrates successful integration of family members who are not biologically linked, but also demonstrates the importance some individuals place on an association with biological parents. Here, too, there may be as much uncertainty about whether such changes would be beneficial or harmful as there is about whether they are likely to occur.

b. Societal obligations. The concept of society's obligation to protect or enhance the health of children and future generations often rests on some notion of an adequate minimum of health care. This benchmark, in turn, depends upon assumptions about what counts as a serious defect or disability, on the one hand, and what constitutes normal functioning or adequate health, on the other. As technological capabilities grow, the boundary between these criteria will blur and shift, and with this will come changes in people's views about what society owes to children and to future generations.

As new technological capabilities raise the standard of normal functioning or adequate health, the scarcity of societal resources may raise anew a very difficult question that theorists of distributive justice have strongly disagreed about: where does justice to future generations end and generosity begin? This question is of vital practical import, for the demands of justice are characteristically thought of as valid claims or entitlements to be enforced by the coercive power of the state, while generosity is usually regarded as a private virtue.

Yet society has traditionally been reluctant to interfere with reproductive choice, at least in the case of competent adults. Even with the advent of genetic counseling and screening social policy has for the most part scrupulously avoided restricting reproductive choice, either as a matter of justice or on any other grounds.[20] So long as the only alternatives are termination of pregnancy or avoidance of conception, any attempt to enforce a public policy designed to prevent genetic defects constitutes a severe infringement on freedom of reproductive choice. If genetic engineering and related reproductive technologies enable a marked reduction of genetic defects and the burden they impose on their victims and on societal resources, however, mandatory genetic treatments may be advocated. Involuntary blood transfusions of pregnant women have been ordered by courts when physicians conclude this is necessary to prevent serious harm to fetuses. Future developments in gene surgery or gene therapy may lead to further departures from the principle that a competent adult may always refuse medical procedures in nonemergency situations and from the assumption that parenting and reproduction are largely private and autonomous activities.

c. The commitment to equality of opportunity. Since the application of the burgeoning recombinant DNA technology will bring benefits as well as costs and since it will be funded at least in part by public resources, it is essential to ask several questions. Who will benefit from the new technology? And will the benefits and costs be distributed equitably?[21] Indeed, what sort of distribution would count as "fair" when the very thing that is being distributed (such as cognitive ability) is itself often the basis for distributing other things of value in society?[22]

The possibilities presented by gene therapy and gene surgery may in fact call into question the scope and limits of a central element of democratic political theory and practice: the commitment to equality of opportunity. One root idea behind the modern concept of equality of opportunity is the belief that because the social assets a person is born with are in no way earned or merited, it is unfair for someone's luck in the "social lottery" to determine that person's most basic prospects in life. Until recently, those who have sought to ground the commitment to equality of opportunity on this belief have only urged that social institutions be designed so as to minimize or compensate for the influence that the "social lottery" exerts on a person's opportunities.[23] Genetic engineering raises the question of whether equality of opportunity requires intervention in the "natural lottery" as well, for people's initial genetic assets, like their initial social assets, are unearned and yet exert a profound influence on opportunities in life. Even to ask this question challenges a fundamental assumption about the scope of principles of distributive justice, namely that they deal only with inequalities in social goods and play no role in regulating natural inequalities.

d. Genetic malleability and the sense of personal identity.

The manipulation of genes that play an important role in regulating processes of growth and aging or that contribute significantly to personality or intelligence--if it ever becomes possible--could have considerable impact on the way people think of themselves. The current tendency is to think of a person as an individual of a certain character and personality that, following the normal stages of physical, social, and psychological development, is relatively fixed within certain parameters. But this concept--and the sense of predictability and stability in interpersonal relations that it confers--could quickly become outmoded if people use gene splicing to make basic changes in themselves over the course of a lifetime. People can already be changed profoundly through psychosurgery, behavior modification, or the therapeutic use of psychoactive drugs. But genetic engineering might possibly provide quicker, more selective, and easier means. Here again, uncertainty about possible shifts in some of people's most basic concepts brings with it evaluative and ethical uncertainty because the concepts in question are intimately tied to values and ethical assumptions. It is not likely that anything so profound as a change in the notion of personal identity or of normal stages of development over a lifetime is something to which people would have clear value responses in advance.

e. Changing the meaning of being human. Some geneticists have seen in their field the possibility of benefit through improving human traits.[24] Human beings have the chance to "rise above [their] nature" for "the first time in all time," as one leader in the field has observed:

> It has long been apparent that you and I do not enter this world as unformed clay compliant to any mold. Rather, we have in our beginnings some bent of mind, some shade of character. The origin of this structure--of the fiber in this clay--was for centuries mysterious....Today...we know to look within. We seek not in the stars but in our genes for the herald of our fate.[25]

Will gene splicing actually make possible such changes in "human nature" for the first time? In some ways this question is unanswerable since there is great disagreement about which particular characteristics make up "human nature." For some people, the concept encompasses those characteristics that are uniquely human. Yet most human genes are actually found in other mammals as well; moreover, recent work by ethologists and other biologists on animal behavior and capacities is demonstrating that many characteristics once regarded as unique to human beings are actually shared by other animals, particularly by the higher primates, although an ability to record and study the past and to plan beyond the immediate future appears to be a singularly human trait.

Other people regard the critical qualities as those natural characteristics that are common to all human beings, or at least all who fall within a certain "normal range." "Natural" here means characteristics that people are born with as opposed to those that result from social convention, education, or acculturation.

To consider whether gene splicing would allow the changing of human nature thus breaks down into two questions. Which characteristics found in all human beings are inborn or have a large inborn basis? And will gene splicing techniques be able to alter or replace some of the genetic bases of those characteristics? As to the first, the history of religious, philosophical, and scientific thought abounds with fundamental disputes over human nature. Without a consensus on that issue the second question could only be answered affirmatively if it were clear that gene splicing will eventually allow the alteration of all natural characteristics of human beings.

As it is by no means certain that it will ever be possible to change the genetic basis of all natural characteristics, it seems premature to assume that gene splicing will enable changes in human nature. At most, it can perhaps be said that this technology may eventually allow some aspects of what it means to be human to be changed.

Yet even that possibility rightly evokes profound concern and burdens everyone with an awesome and inescapable responsibility--either to develop and employ this capability for the good of humanity or to reject it in order to avoid potential undesirable consequences.

The possibility of changing human nature must, however, be kept in perspective. First, within the limits imposed by human beings' genetic endowment, there is already considerable scope by means other than gene splicing for changing some acquired characteristics that are distinctively human. For example, people's desires, values, and the way they live can be changed significantly through alterations in social and economic institutions and through mass education, indoctrination, and various forms of behavior control. Thus, even if gene splicing had the power that some people are concerned about, it would not be unique in its ability to produce major changes in what it means to be human--although it would be unusual in acting on the inheritable foundation of thoughts and actions. If the technology can ever be used in this way, the heritability of the changes ought probably to regarded as significantly different from any changes now possible.[26]

Second, according to the theory of evolution, the genetic basis of what is distinctively human continually changes through the interplay of random mutation and natural selection. The concern, then, is that gene splicing will for the first time allow deliberate, selective, and rapid alterations to be made in the human genetic constitution.

Finally, concern about changing human nature may at bottom be still more narrowly focused upon those characteristics of human beings--whether unique to the species or not--that are especially valued or cherished. Here, too, there may be disagreement as to which characteristics are most valuable and the value of a given characteristic may depend upon the social or natural environment in which it is manifested.

In sum, the question of whether gene splicing will enable changes in human nature--and the ethical, social, and philosophical significance of such changes--cannot be determined until much more is known about human genetics, specifically the exact contribution of heredity to many human physical and, more important, behavioral traits. Indeed, one of the most important contributions genetic engineering could make to the science of behavioral genetics may be that it will help resolve the age-old controversy of nature versus nurture. If designed changes were possible, society would have to confront whether such changes should be made, and, if they should, which ones. The problems created by uncertainty are particularly notable here since any decision about what characteristics are "desirable" would depend on the world that people will be living in, which is itself unknowable in advance.

f. Unacceptable uses of gene splicing. A recent National Science Foundation survey indicates that though Americans are generally against restrictions on scientific research, "a notable exception was the opposition to scientists creating new life forms." The survey notes that

> Almost two thirds of the public believe that studies in this area should not be pursued. Fear of the unknown and of possible misuse of the discoveries by some malevolent dictator are among the reasons that could be given for opposition to such genetic engineering.[27]

Given the excesses of the eugenics movement in the United States and elsewhere in the early decades of this century and the role of eugenic theory in mass atrocities perpetrated by the Nazis, these fears cannot be dismissed as groundless. Some comfort may be drawn from the fact that although the possibility of directing human inheritance through simple breeding techniques has existed for centuries, it has not, with relatively minor exceptions, been attempted. Furthermore, the peculiar social and political circumstances that led to these attempts to control human reproduction through the coercive power of the state are not present in this country and are unlikely to occur in the foreseeable future.

Reassuring though they are, these answers are far from conclusive. Government control of sexual reproduction on a broad scale--through an enforced scheme for mating human beings--would require enormous repressive power and social control over individuals over an extended period of time. What might prove more tempting to a dictator or authoritarian ruling elite is the possibility of scientists rapidly making major changes in the genetic composition of a small group in the privacy of the laboratory.

Though there appears at present to be no evidence that the government of this or any other country is attempting to use gene splicing for unacceptable political purposes, the Commission believes that the appropriate posture for the public and the scientific community is one of vigilance. The best safeguards against such abuses are a continued support of democratic institutions and a commitment to individual rights combined with public education about the actual and potential uses of gene splicing technology. Of course, such efforts in this country would not avoid undesirable uses of genetic engineering by totalitarian governments, unless they led to effective international restrictions.[28]

A more subtle danger is that if genetically engineered changes ever become relatively easy to make, there may be a tendency to identify what are in fact social problems as genetic deficiences of individuals or to assume that the appropriate solution to a given problem, whether social or individual, is genetic manipulation.[29] The relative ease of genetic methods (if gene therapy becomes an accepted medical technique) should most certainly not draw attention away from the underlying social causes of such problems.

g. Distributing the power to control gene splicing. Beyond any fear of the malevolent use of gene splicing, attention must be paid to a more basic question about the distribution of power: who should decide which lines of genetic engineering research ought to be pursued and which applications of the technology ought to be promoted?

This question is not ordinarily raised about medical technology in general. When it is, the assumption is that for the most part the key decisions are to be made by the relevant experts, the research community, and the medical profession, guided by the availability of research funds (which come predominately from Federal agencies) and by the dictates of medical malpractice law and of state and Federal regulatory agencies designed to protect the public from very tangible, unambiguous harms. Yet genetic engineering is more than a new medical technology. Its potential uses, as discussed, extend far beyond intervention to cure or prevent disease or to restore functioning. This more expansive nature makes it unlikely that decisions about the development of gene splicing technology can be made appropriately within institutions that have evolved to control medical technology and the practice of medicine.

Clearly, adequate institutional arrangements for decisionmaking about the further development of gene splicing technology must assign a substantial role to experts in the field. Yet it is important to understand the unavoidable limitations of technical expertise. On the one hand, there are the limitations of the experts' knowledge; on the other, there are the limitations of technical knowledge itself, no matter how thorough. Experts in genetic engineering can provide the most accurate available data, from which probability statements can be formulated. But neither geneticists nor scientists experienced in risk assessment have any special expertise about evaluative and conceptual uncertainties. An expert might conclude that there is a 5% probability that a certain harmful outcome will occur, but that knowledge is not sufficient for deciding whether such a probability is an acceptable degree of risk. Nor can scientific expertise answer the question of whether the burdens of risk would fall disproportionately upon some people, for this is a moral, not a scientific, question. This is not to say, of course, that scientific experts should not make moral judgments or that if they do they ought to be ignored. But the limitations of expertise must be clearly understood.

In general the public can reasonably rely on the judgments of experts in the field to the extent that at least three conditions are satisfied: (1) there is a strong consensus among the experts, (2) the process by which individuals come to be identified as experts is not unduly influenced by political factors or other forces unrelated to their qualifications as experts, and (3) the experts are not subject to serious conflicts of interest that are likely to distort their judgments or to make their advice unreliable.[30] Whether, or to what extent, these conditions are satisfied cannot be answered once and for all. Instead, they must be viewed as useful rules-of-thumb for assessing and reassessing the role of experts in the formation of responsible public policy.

h. Commercial-academic relations. Concern over the latter two points--unacceptable uses of the technology and the power of control it--have contributed to a growing public debate about the increased commercial involvement with university-based research on gene splicing. Constraints on support for basic science research by the Federal government in the past decade have been compounded by economic problems that have reduced both state budgets for higher education and the grants of philanthropic foundations. Consequently, academic research scientists are turning increasingly to industry,[31] forming ties that have raised concern about how to accommodate the divergent goals and norms of science and industry.

Universities have historically been dedicated to increasing the general fund of knowledge through basic research, the open exchange of information and ideas, and the training of new researchers and scholars. These goals may run headlong into those of industry--the development of marketable products and techniques through applied research by maintaining a competitive posture, protecting trade secrets, and seeking patent protection.

The conflicts occasioned by these developments are not unique to genetic engineering; indeed, at the beginning of this century a number of expanding universities shifted their focus from the traditional arts and sciences as they became allied with the burgeoning electrical and chemical industries. Medicine, agriculture, econometrics, solid state physics, and computer science have all been advanced in part because of combined forces of industry and universities. Yet the recent similar developments in biotechnology present these issues in sharper relief for several reasons.

First, commercialization of biotechnology seems to be proceeding more rapidly than in chemistry and physics. And in gene splicing, the gap between theory and application--between a graduate student's work in the lab and a highly lucrative product--is often quite small. Finally, the range of potential applications of the research is very broad.

Increased private funding for bioengineering research has therefore sparked questions about conflicts of interest and about the impact of commercialization on academe more generally.[32] Some see these issues as private concerns relating only to the particular universities and firms contracting with each other, a view reflected at a recent conference at Pajaro Dunes when university officials and industry representatives met in private to discuss concerns about commercialization. The participants at this privately funded conference of 5 leading universities and 11 corporations issued a statement intended to "get some general principles on the record" and "set an agenda for further discussion of the issues." The document raised questions of contract review and disclosure, exclusive licensure, and conflicts of interest encountered by university and faculty. It encouraged university faculties to continue examination of these issues over which commentators have noted that "[p]luralism and a certain measure of confusion prevail."[33]

Other issues are also at stake: Can professional virtue be maintained in the face of considerable financial temptations? How will private funding change professors' outlooks?[34] Will fewer be interested in teaching undergraduates? Will they encourage graduate students to focus on projects with maximum commercial potential, instead of those that would foster a more well rounded background? Will commercialization effect a shift from basic to applied research and, if so, with what consequences? Will the secrecy required by industry impede the free exchange of scientific information? What about conflicts of interest when the same academic department includes owners or employees of competitive bioengineering ventures? Will academic appointments and promotions be skewed to favor those who can attract private research funds to the university?

The Association of American Universities has recently suggested that it become a clearinghouse for information on commercialization.[35] These and related questions have also been the subject of debate in the press and before Congressional committees. Undoubtedly, such concerns spill over into the public arena when the question is whether the new agreements are "skimming off the cream produced by decades of taxpayer funded work," as Rep. Albert Gore, Jr., put it in opening Congressional hearings on the subject.[36] Only a continuing public debate over these as-yet-unresolved questions on the commercialization of biotechnology can ensure that the public's interests are being met--its interest in the integrity and credibility of scientific research, in a sound and balanced research agenda, and in the wise expenditure of Federal research dollars.

C. Continuing Concerns

A distinction has been drawn in this Report between two views: (1) that gene splicing technology is intrinsically wrong or contrary to important values and (2) that, while the technology is not inherently wrong, certain of its applications or consequences are undesirable. Regarding the latter, it has also been noted that genetic engineering involves an array of uncertainties beyond those usually found in technological developments. Not only is the occurrence of specific desirable or undesirable consequences impossible to predict but the application of gene splicing could have far-reaching and unpredictable consequences that could alter basic individual and social values.

The Commission could find no ground for concluding that any current or planned forms of genetic engineering, whether using human or nonhuman material, are intrinsically wrong or irreligious per se. The Commission does not see in the rapid development of gene splicing the "fundamental danger" to world safety or to human values that concerned the leaders of the three religious organizations.[37] Rather, the issue that deserves careful thought is: by what standards, and toward what objectives, should the great new powers of genetic engineering be guided?

Even though the many issues raised by gene splicing in human beings need to be considered one by one if their potential consequences are to be clearly assessed, it would be a mistake to compartmentalize the issues.[38] Although the Commission has not found any ethical, social, or legal barriers to continued research in this field, there remains an important concern expressed by the warning against "playing God." It not only reminds human beings that they are only human and will some day have to pay if they underestimate their own ignorance and fallibility; it also points to the weighty and unusual nature of this activity, which stirs elusive fears that are not easily calmed.

At this point in the development of genetic engineering no reasons have been found for abandoning the entire enterprise--indeed, it would probably be naive to assume that it could be. Given the great scientific, medical, and commercial interest in this technology, it is doubtful that efforts to foreclose important lines of investigation would succeed. If, for example, the United States were to attempt such a step, researchers and investment capital would probably shift to other countries where such prohibitions did not exist. To expect humanity to turn its back on what may be one of the greatest technological revolutions may itself betray a failure to recognize the limits of individual and social self-restraint. Even if important lines of research in this country or elsewhere could be halted, to do so would be to run a different sort of risk: that of depriving humanity of the great benefits genetic engineering may bring.

Assuming that research will continue somewhere, it seems more prudent to encourage its development and control under the sophisticated and responsive regulatory arrangements of this country, subject to the scrutiny of a free press and within the general framework of democratic institutions. In light of the potential benefits and risks--uncertain though they may be at this point--a responsible social policy on genetic engineering requires the cooperation of many institutions and organizations.

Efficient regulation and oversight will require considerable division of responsibility among different bodies and agencies. Legal controls will necessarily focus on the prevention of tangible harms to individuals and the environment. Nonetheless, the Commission believes it is crucial that those entrusted with such oversight and regulation do not lose sight of the more elusive, but equally important, concerns about the human significance of genetic engineering or neglect such concerns because they do not fit neatly into existing institutional jurisdictions. The continued development of gene splicing approved in this Report will require periodic reassessment as greater knowledge is gained about the ethical and social, as well as the technical, aspects of the subject.

FOOTNOTES

1. Office of Technology Assessment, Impacts of Applied Genetics--Micro-Organisms, Plants, and Animals, U.S. Congress, U.S. Government Printing Office, Washington (1981); Congressional Research Service, Genetic Engineering, Human Genetics, and Cell Biology--Evolution of Technological Issues, Report Prepared for the Subcommittee on Science, Research and Technology of the House Committee on Science and Technology, Library of Congress, U.S. Government Printing Office, Washington (1976). See also Chapter One supra, text accompanying notes 7-15.

2. Ted Howard and Jeremy Rifkin, Who Should Play God?, Dell Publishing Co., Inc., New York (1977).

3. See Appendix B, pp. _____-_____ infra.

4. See Appendix D, pp. ______-______ infra, for a listing of the religious commentators.

5. Seymour Siegel, Genetic Engineering, in Proc. of the Rabbinical Assembly of America, New York (1978) at 164.

6. In the Biblical tradition of the major Western religions, the universe and all that exists in it is God's creation. In pagan religion, the gods inhabit nature, which is thus seen as sacrosanct, but the Biblical God transcends nature. However, since God created the world, it has meaning and purpose. God has placed a special being on earth--humans--formed in the image of God and endowed with creative powers of intelligence and freedom. Human beings must accept responsibility for the effects brought about by the use of the great powers with which they have been endowed--for the betterment of the world--to uncover nature's secrets.

7. As Science journalist Nicholas Wade has observed:

> We are about to enter an explosive phase of discovery in which we are going to reach close to the great goal of Western inquiry: the complete understanding of man as a physical-chemical system.

NOVA, Life: Patent Pending, WGBH Transcripts, Boston (1982) at 24.

8. Pope John Paul II, who had earlier been critical of genetic engineering, recently told a convocation on biological experimentation of the Pontifical Academy of Science of his approval and support for gene splicing when its aim is to "ameliorate the conditions of those who are affected by chromosomic diseases" because this offers "hope for the great number of people affected by those maladies."

> I have no reason to be apprehensive for those experiments in biology that are performed by scientists who, like you, have a profound respect for the human person, since I am sure that they will contribute to the integral well-being of man. On the other hand, I condemn, in the most explicit and formal way, experimental

> manipulations of the human embryo, since the human being, from conception to death, cannot be exploited for any purpose whatsoever....I praise those who have endeavoured to establish, with full respect for man's dignity and freedom, guidelines and limits for experiments concerning man.

Pope John Paul II, La sperimentozione in Biologia deve contribuire al bene integrale dell'uomo, L'Osservatore Romano, Rome, Oct. 24, 1982, at 2.

9. Robert L. Sinsheimer, Genetic Research: The Importance of Maximum Safety and Forethought (Letter), N.Y. Times, May 30, 1977, at 14.

10. Despite the great attention paid to the "biohazards" of the research with, and products of, gene splicing, the Environmental Impact Statement filed by NIH on its RAC guidelines focuses on the health effects on humans, plants, and animals and does not deal with ecosystems as entities. Subsequently, however, the Environmental Protection Agency has supported research on the effects of introducing recombinant organisms on the stability of various ecosystems.

11.

> [W]hat made the Gallilean and the other major scientific revolutions disturbing is the reductionism, that we become less than what we are. [T]hat is what is so uncertain about gene therapy, because it gets back to a very fundamental question..."Is there anything unique about humans?"
>
> And if there isn't anything unique about humans, there's nothing wrong with doing gene manipulation. But if there is something unique about humans, then it is wrong to pass over the barrier, wherever the barrier is--but we don't know where the barrier is.
>
> But as soon as you ask, "Where is the barrier?" you ask, "Is there a barrier?" And that's frightening. If there's nothing unique about humans--that's not a theological question but a very real one.

Testimony of French Anderson, M.D., transcript of 22nd meeting of the President's Commission (July 10, 1982) at 115-16.

12. As one physician-scientist has remarked, "We must all get used to the idea that biomedical technology makes possible many things we should never do." Leon Kass, The New Biology: What Price Reducing Man's Estate?, 174 Science 779 (1971).

13. If there is any special concern in the evaluation of the products of gene splicing, it is only that in the initial stages of any new process there are uncertainties about some effects of the process. For example, bacterial contaminants are a unique by-product of gene splicing and in testing human insulin it was important to determine whether these contaminants induced deleterious antibodies in humans.

14. See note 10, Chapter Two supra, and accompanying text.

15. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, Screening and Counseling for Genetic Conditions, U.S. Government Printing Office, Washington (1982).

16. "Have we the right to counteract, irreversibly, the evolutionary wisdom of millions of years, in order to satisfy the curiosity of a few scientists? The future will curse us for it." Liebe F. Cavalieri, New Strains of Life--Or Death, N.Y. Times, Aug. 22, 1976 (Magazine), at 8, 68 (quoting Erwin Chargaff).

17. Stephen Stitch, The Recombinant DNA Debate, 7 Phil. & Pub. Aff. 187 (1978).

18. See p. II-20 supra. Carriers of recessive diseases are people who possess one normal and one variant gene; they usually show no deleterious effects and may, as in the case of sickle-cell, have an advantage. The sickle-cell advantage is, however, dependent on time and place. In a temperate, nonmalarial area, or in a tropical climate from which the malaria parasite has been eliminated, carrying the sickle-gene would not confer an advantage.

19. A.M. Capron, The Law of Genetic Therapy in Michael P. Hamilton, ed., The New Genetics and the Future of Man, William B. Eerdmans Publishing Co., Grand Rapids, Mich. (1972) at 133, 140 (raising question of a need for a living "genes savings bank").

20. Screening and Counseling for Genetic Conditions, supra note 15, at xx.

21. More specifically, it is important to ask whether the further development of gene splicing will reinforce or perhaps exacerbate existing social, cultural, and economic inequalities. This factor explains part of the concern that has been expressed about who will control this technology. Although objections have focused on corporations controlling access (through trade secrets and patents), Howard and Rifkin, supra note 2, at 189-207, the greatest abuses of genetics have involved governmetnal decisionmaking. Kenneth M. Ludmerer, Genetics and American Society: A Historical Appraisal, Johns Hopkins Univ. Press, Baltimore (1972) at 121-34.

22. Suppose, for example, a society distributes certain scarce resources on the basis of merit--e.g., intelligence, diligence, physical abilities. What if intelligence could be engineering upward? Who would merit this increase in merit? The very oddity of the inquiry calls into question the continued use of intelligence as a basis for resolving competing claims--say, for admission to educational institutions or for access to the intelligence-raising technology itself. We could resort to the other coexisting merit attributes--unless

> they too were alterable by design. Under these conditions, how could we retain our system of merit distribution? If we could not, how would we then distribute the resources? By resort to a standard of efficiency? By leaving matters to a market? Or by designing a lottery?

Michael H. Shapiro, Introduction to the Issue: Some Dilemmas of Biotechnology Research, 51 S. Cal. Law R. 987, 1001-02 (1978) (citations ommitted).

23. John Rawls, A Theory of Justice, Harvard University Press, Cambridge, Mass. (1973) at 83.

24. Herman J. Muller is the scientist most associated with this view. In the mid-1960s he viewed selective breeding as a method for "a much greater, speedier, and more significant improvement of the population" than any direct rearrangement of genetic material possible in the 21st century. He advocated giving women "germinal choice" through artificial insemination of them with the genes for superior traits. Herman J. Muller, Means and Aims in Human Genetic Betterment, in T.M. Sonneborn, ed., Control of Human Heredity and Evolution, Macmillan Co., New York (1965) at 100. The list of the traits found desirable by Professor Muller changed dramatically over time, as did the types of individuals whose sperm should be used--Lenin appeared on the first list but disappeared during the Cold War. Garland E. Allen, Science and Society in the Eugenic Thought of H.J. Muller, 20 BioScience 346 (1970).

25. Robert L. Sinsheimer, The Prospect of Designed Genetic Change, 32 Engineering and Science 8, 13 (April 1969). Prof. Sinsheimer took a different view from Prof. Muller. He contrasted the "older eugenics" of breeding, which would require a "massive social program," with the new eugenics that could permit "conversion of all the unfit to the highest genetic level" and "could, at least in principle, be implemented on a quite individual basis, in one generation, and subject to no existing social restrictions." Id. Prof. Sinsheimer subsequently became very doubtful about the wisdom of changing genes. See note 19, chapter 1, supra.

26.

> If any one age really attains, by eugenics and scientific education, the power to make its descendants what it pleases, all men who live after it are patients of that power. They are weaker, not stronger: for though we may have put wonderful machines in their hands we have pre-ordained how they are to use them....The real picture is that of one dominant age...which resists all previous ages most successfully and dominates all subsequent ages most irresistibly, and thus is the real master of the human species. But even within this master

> generation (itself an infinitesimal minority of the species) the power will be exercised by a minority smaller still. Man's conquest of Nature, if the dreams of the scientific planners are realized, means the rule of a few hundreds of men over billions upon billions of men.

C.S. Lewis, The Abolition of Man, Collier-Macmillan, New York (1965) at 70-71.

27. John Walsh, Public Attitudes Toward Science is Yes, but--, 215 Science 270 (1982) (quoting National Science Foundation, Science Indicators 1980).

28. Another misuse of gene splicing with international ramifications, described by the World Council of Churches as a "grave hazard," is "the deliberate production of pathogenic micro-organisms for biological warfare or terrorism." Paul Abrecht, ed., 2 Faith and Science in an Unjust World: Report of the World Council of Churches' Conference on Faith, Science and the Future, Fortress Press, Philadelphia (1980) at 53.

29. "In discussing the use of any science, including genetics, to solve social problems, it...becomes important to demarcate clearly the limit that scientific technique may be expected to contribute to an effective solution." Ludmerer, supra note 21, at 180. To take an extreme example, in a society in which gene surgery was widely used and accepted, it might be tempting to "solve" the problem of racial discrimination by making genetic changes to eliminate dark skin. A less fanciful example would be the decision to make genetic alterations in certain groups of workers who are exposed to dangerous chemicals in the workplace rather than to eliminate the dangers.

> Moreover, genetic research may denigrate the value that society has perceived in the moral and autonomous aspects of human conduct by forcing society to question the limits of free will and self-determination. Thus, genetic research has the power to reorder society's priorities and restructure its values; fundamentally, it can change the structures of human thought and the social construction of reality.

Marc Lappé and Patricia Archbold Martin, The Place of the Public in the Conduct of Science, 52 S. Cal. L. Rev. 1535, 1537 (1978) (citations omitted).

30. See Stitch, supra note 17.

31. Estimates have put industry support of academic research at about $200 million per year. Although this represents only about 4% of what government contributes, it is a growing proportion. The formation in the past decade of about 200 new private ventures to pursue research and development in genetic engineering has been paralleled by increased interest on the part of existing industrial firms in universities that have strong programs in molecular biology. This interest has been capped by several well-publicized multimillion dollar agreements.

32.
> That journey of discovery can only be undertaken once, and it would be better undertaken by people who have no interest in anything other than discovering the truth, whose hands are clean, whose motives can never be criticized. That's in the public's interest; that is in science's true interest. And if the commercialization, if this secondary goal of getting rich, ever starts to influence a scientist's primary goal, a university's primary goal of discovering the truth, then the scientists themselves, I hope, will have the sense to put a halt to it.

Wade, *supra* note 7, at 24-25.

33. Barbara J. Culliton, *Pajaro Dunes: The Search for Consensus*, 216 Science 155 (1982); Draft Statement Pajaro Dunes Conference (March 25-27, 1982).

34. One physician-scientist who formerly held high budgetary and science advisory positions in the Federal government and who is presently the Dean of a school of public health has suggested that the financial agreements between universities and medical school faculty in the clinical departments could be "at least partially relevant" in finding a means of protecting the research and educational commitments of the basic-science faculties while generating added income. Gilbert S. Omenn, *Taking University Research into the Marketplace*, 307 New Eng. J. Med. 694, 699-700 (1982).

35. Letter from Robert M. Rosenzweig, chairman of the Association of American Universities Committee on University/Industry Relations, to Reps. Don Fuqua and Albert Gore, Jr. (Oct. 28, 1982) (on report of AAU study group).

36. Commercialization of Academic Biomedical Research, Hearings before the Subcomm. on Invest. and Oversight and the Subcomm. on Science, Research and Tech. of the House Comm. on Science and Tech., 97th Cong., 1st Sess., June 8, 1981, at p. 2.

37. See Appendix B, at pp. xxx-yyy *infra*.

38.
> The predominant methodological strategy of biological research is reductionism: the isolation of the phenomenon under study from its usual circumstances, thereby reducing the number of variables that affect the analysis. This allows a clearer understanding of the "basic" processes, and has led to important discoveries.
>
> The strength of reductionism is the principle of isolation. This principle, however, is also inherently limiting: the circumstances of the investigation are necessarily 'unreal' in everyday terms. Of course, it may be that the isolated phenomena behave similarly under natural circumstances. This assumption, however, is often uncertain and may frequently be untrue. Moreover, the characterisstics of those natural circumstances are rarely fully known. In some cases, knowledge of the multiple external

> influences upon biological processes could lead to a perception of those processes quite different from those obtained in the isolation of laboratory study. A critical understanding of present biological knowledge requires recognition of those methodological weaknesses. Public participation in science, by broadening the range of factors considered at each stage of investigation, provides a means of counteracting biases resulting from reductionist strategy.

Halsted R. Holman and Diana B. Dutton, A Case for Public Participation in Science Policy Formation and Practice, 51 S. Cal. L. Rev. 1505, 1513-14 (1978) (citation omitted).

CHAPTER 4: PROTECTING THE FUTURE

The material presented in the earlier chapters provides the basis for the Commission's recommendations on the means through which the issues generated by genetic engineering can continue to receive appropriate attention. These issues are not matters for a single day, deserving of only occasional attention. They will be of concern to the people of this country--and of the entire globe--for the foreseeable future; indeed, the results of research and development in gene splicing will be one of the major determinants of the shape of that future. Thus, it is important that this field, with its profound social and ethical consequences, retain a place at the very center of "the conversation of mankind."[1]

Specifically, in the preceding material the Commission has seen that:

(1) The careful attention paid by scientists, private groups, and government officials to the immediate health and environmental risks has been rewarded with a record of safe and fruitful research and development.

(2) Although the Federal Interagency Committee on Recombinant DNA Research has been inactive for several years, the Recombinant DNA Advisory Committee (RAC) at the National Institutes of Health (NIH) has provided an informal means for intragovernmental communication, as well as overseeing the safety of NIH-funded research.

(3) The issues raised by the projected human uses of gene splicing, which heretofore have not received attention, are as at least as complex and important as those addressed by RAC thus far.

(4) These issues would benefit from an evaluation process that is continuing rather than sporadic, to allow a review body to develop coherent standards and orderly procedures, while making provisions for unexpected developments in gene splicing and other changes in the world at large.

(5) It would be desirable to develop means for such an evaluation process now, not because of any threat of imminent harm but because the issues are better addressed in anticipation rather than in the wake of a possible untoward or unforeseen outcome.

(6) The issues are so wide-ranging as to require a process that is broad-based rather than primarily expert, since the issues cannot be resolved on technical grounds alone and since many of the most knowledgeable scientists are deeply involved in the field as researchers or even as entrepreneurs.

These observations do not, of course, point to any single framework for a continuing oversight of this area. Because of its large role in funding biomedical research and its statutory responsibilities to ensure that environmental, industrial, and pharmaceutical safety standards are being met, the Federal government will be a participant in any well-designed process of planning and review. But this function need not be regarded as exclusively governmental. A variety of organizations in the private sector--such as the American Association for the Advancement of Science, the National Academy of Sciences, the Industrial Biotechnology Association, and the Pharmaceutical Manufacturers Association--could well play important leadership and educational roles.

Finally, within the governmental sector, the responsibility for oversight--not only coordinating what is being done but also identifying what still needs to be done--is very important. It, too, can be supplied by a variety of means, including Congressional committees and the Office of Technology Assessment. Or the body charged with overall responsibility might also have direct regulatory power, as opposed to the authority to stimulate appropriate actions on the part of those agencies that do have the power.

A. Objectives

The President's Commission believes that the design of any oversight group should be guided by several objectives. First, the group should regard education as a primary responsibility. It is necessary to educate the scientific community about the social and ethical implications of its work as well as to educate the public about science.

Second, the group should have roles both of general oversight and of leadership within the Federal government. For this, it will need direct access, through liaison arrangements, to all Federal departments or agencies with a large stake in sponsoring, regulating, or scrutinizing work in this field. At a minimum it should possess "action-forcing power," whereby departments and agencies are required to publish its regulatory recommendations for comment in the Federal Register within a specified time and then either to adopt or reject the recommendations, with an explanation likewise published in the Federal Register.

Third, the body should be capable of leading, as well as reflecting, public thinking on the important issues before it; it can serve as an intermediary between biomedical scientists and the public, helping to translate and clarify the ideas and concerns of each for the other. To do so, it will need diverse membership.[2] It also ought to conduct its work in public and seek to have it widely disseminated. A policy-making process that draws on nonscientists and avoids unnecessary secrecy is likely not only to lead to better results but also to inspire much greater public confidence in, and support for, research efforts themselves.[3]

Fourth, it should strive to operate on scientifically sound premises. For this it will need a means of drawing on groups of scientists for advice and explanation in a way that does not lead it to be dominated by the scientific community.

Fifth, it should treat--in as unified a framework as possible--all the issues raised by genetic engineering: laboratory and industrial safety, environmental hazards, agricultural and commercial opportunities and pitfalls, international ramifications, biomedical benefits and risks, and social and ethical implications.

Sixth, insofar as possible, the oversight functions should be separated from any sponsoring functions, so that no conflicts of interest, of the sort that plagued the Atomic Energy Commission, will arise.

B. Revising RAC

RAC, which had been created in October 1974 as a scientific and technical committee, was subsequently made into a more representative body by HEW Secretary Joseph Califano, through the addition of nonscientific members of the public. Recently, Dr. Donald Fredrickson, who presided over the transformation as the Director of NIH, suggested that the time for a "third generation" RAC may have arrived.[4] The President's Commission concurs, since there is plainly great value in building on the history--largely regarded as successful--of RAC. Design of an appropriate body for the task will require consideration of many factors, some of which (such as funding) are beyond the purview of the President's Commission.[5] But as a starting point, it may be helpful if the Commission suggests possible formats for consideration by the President and Congress.[6]

One means of supplementing RAC, now that it is less active since the laboratory biohazards are no longer regarded as urgent matters, would be through a mixed public-private sector body established outside the Federal government.[7] This format has been employed in the initial work in other fields and there are plainly many organizations, ranging from those with academic and commercial interests to the religious bodies that prompted the present study, from which such a group could draw.

If it is felt that the extent of Federal responsibility is so great, both for safety and for promotion of this field, that a governmental body of greater breadth than the present RAC is needed, the Interagency Committee established in 1976, which has been inactive for the past several years, could be reinvigorated.[8] This would have the advantage of direct involvement of the leading Federal agencies but the disadvantage that its membership is entirely governmental and its meetings are not subject to the Federal Advisory Committees Act.

Rather than creating additions to RAC, it might be preferable to redesign it. The greater scope of work for the new RAC would have two aspects. First, the range of issues must certainly be broadened beyond laboratory and manufacturing hazards. Second, the involvement of other Federal bodies must be greater. Placing the successor to RAC outside of any one department should promote this end, without making it merely a group of Federal agency representatives.[9]

One format would be the creation of a Genetic Engineering Commission (GEC) of 11 to 15 members from outside the government that would meet regularly to deal solely with this field. This group could have a majority of nonscientists--members of the general public as well as experts in ethics and philosophy, law, the social and behavioral sciences, and public and private management. In addition to a small staff, the GEC could have a series of Technical Panels that could provide expertise in (1) laboratory research; (2) agricultural and environmental uses and dangers; (3) manufacturing concerns; (4) human uses; and (5) international controls. It should also be able to draw on a panel of liaison officers from the Departments of Agriculture, Commerce, Defense, Energy, Health and Human Services (one each from the Centers for Disease Control, the National Institutes of Health, the Food and Drug Administration, and the National Institute for Occupational Safety and Health), Interior, Labor (including one from the Occupational Safety and Health Administration), and State; the National Science Foundation; the National Endowment for the Humanities; and the Environmental Protection Agency.

An alternative format would be to assign responsibility for oversight of genetic engineering to the body that succeeds the President's Commission.[10] This arrangement could have some advantages. Principally, it would permit the continuing oversight of gene splicing to be integrated into the consideration given to the social, legal, and ethical implications of other important developments in the biomedical arena. Also, it would recognize that the flow of work for such a body is not always at an even pace; a group with a more diverse mandate, such as the President's Commission, could turn its attention to other areas rather than wasting time when there are no gene splicing issues needing attention, while still being ready should such issues need prompt attention.

Giving the assignment to the present Commission's successor might have several disadvantages, however. First, it seems unlikely that there will be any paucity of items to consider; in addition to the work presently performed by RAC, the agenda of any new body would be augmented by the many issues that RAC has felt were beyond its mandate. Second, not all the issues are ones of "bioethics," and assigning the task to the President's Commission might narrow the range of issues to be considered. (For example, in the present study, the Commission did not feel it had a basis for making judgments on the issues of patents and trade secrets, although they are important questions for the future of genetic engineering.) Third, by focusing primarily on genetic engineering, a GEC would be better able to develop among its members and staff the necessary familiarity with all the major issues and the underlying science.

Whatever mechanism is adopted, from among these or others, the quality and diversity of the members appointed to such a body, as well as the processes through which it deliberates, will be central determinants of its success. Whether the body is given formal regulatory powers, or merely the authority to issue guidelines and give advice, its major impact will rest on its ability to educate and to persuade. It must set its sights high if it is to function as "an agency for the protection of the future."[11] To protect the future people must sometimes be willing to act with vision and spirit as well as with humility--and striking a balance between courage and prudence is never easy.

FOOTNOTES

1. Michael Oakeshott, *The Voice of Poetry in the Conversation of Mankind*, in Rationalism in Politics and Other Essays, Metheun, London (1962) at 197.

2.

> One well-known investigator has urged: "If this investigation [work in genetic engineering] is done with man, the study should be made with collaborators who can protect genetics from public scorn by having scientists working with articulate sociologists and psychologists who plan for a long time before doing the engineering."

Kenneth M. Ludmerer, Genetics and American Society: A Historical Appraisal, Johns Hopkins University Press, Baltimore (1972) at 179 (quoting Dr. Clarence P. Oliver).

3.

> If this industry follows the path that appears easier initially, the cloistered avoidance of other forces of society, it will pay a penalty years hence should some event force a public inquiry.

George E. Brown, Jr., *The Policymaking Challenge of the Bioengineering Industry*, 4 Recombinant DNA Technical Bull. 121, 123 (1981). Rep. Brown, former chairman of the House Subcommittee on Science, Research, and Technology, has urged the commercial concerns in the genetic engineering field to establish public trust by forming an "active" and "open" industrial council to exercise powers of censure, laboratory approval, and similar functions. *Id.* at 122.

> But there needs to be a broader entity, at least initially. There should be a council with a broad and diverse membership to look at the entire range of issues that a genetic engineering industry raises. Scientists, lay people, lawyers, policymakers, regulators, clergy, and other groups should be represented in a council of manageable size....There will be objections to the inclusion of nonscientists on the panel deciding scientific matters. These have been heard before but experience has shown that these people become valuable contributors.
>
> ...Knowing the aversion that researchers have to being burdened by broad social and ethical considerations, I would understand a reluctance by researchers to willingly submit to what would undoubtedly be a time consuming discussion. But these views will be present in any public debate and are better incorporated sooner than later.

Id. at 123.

4. Joseph G. Perpich, *Industrial Involvement in the Development of NIH Recombinant DNA Research Guidelines and Related Federal Policies*, 5 Recombinant DNA Technical Bull. 59, 77 (1982) (quoting a talk by Dr. Fredrickson, *rDNA Controversy: The NIH Viewpoint*, delivered at the annual meeting of the American Association for the Advancement of Science, January 7, 1982, to be published in a volume edited by Raymond Zalinskas and Burke Zimmerman).

> The idea . . . is to make RAC more representative of both the scientific and regulatory communities as well as the public to be better equipped to deal with the emerging problems and be relieved of some of the detailed burden of reviewing minor administrative concerns. Such a "third generation" RAC should be accountable to a Cabinet officer . . .
>
> The concept was instantly adopted, at least in principle, by Dr. Ray Thorton, chairman of RAC and a fellow panelist at AAAS.

"Third Generation" of RAC Suggested by Dr. Fredrickson, 2 Genetic Engineering Letter 1 (1982).

5. In Diamond v. Chakrabarty, 447 U.S. 303 (1980), the Supreme Court reached a similar conclusion about the competence of the judiciary to decide, within the context of a patent case, the merits of the contention of the Federal government and various *amici curiae* that genetic engineering presented "grave risks" of "pollution and disease,...loss of genetic diversity, and...depreciat[ion of] the value of human life." The Court found that deciding whether the research "may pose a serious threat to the human race" or that such concerns were "fantasies generated by fear of the unknown" was a matter for Congress and the Executive.

> The choice we are urged to make is a matter of high policy for resolution within the legislative process after the kind of investigation, examination, and study that legislative bodies can provide and courts cannot. That process involves the balancing of competing values and interests, which in our democratic system is the business of elected representatives.

Id. at 317. The Commission has tried to advance the process of "investigation, examination, and study" but the ultimate "balancing of competing values and interests" is for elected officials.

6. These suggestions draw on the work of the Federal Interagency Committee on Recombinant DNA Research, which was created at the direction of President Ford in 1976. That Committee recommended the adoption of legislation explicitly to regulate recombinant DNA research, in light of the disjointed fashion in which existing legislation touched on the field. President Carter endorsed the resulting legislation, which was drafted by the Department of Health, Education, and Welfare. It was introduced in

Congress by Senator Edward M. Kennedy and Representative Paul G. Rogers. As redrafted by his health subcommittee after hearings, Senator Kennedy's bill called for the creation of an 11-member Presidential Commission (with 5 scientific and 6 lay members); the House version would have created a 15-person advisory committee to the Secretary of HEW.

7. Corporate lawyer Milton Wessel has argued for the value, as a general matter, of institutions involved with science and technology pursuing a "rule of reason" in place of the adversary approach to the country's emerging socioscientific problems. If the private sector does not take the lead in resolving these emotion-laden issues in a fashion that serves the public interest, he believes the public will demand much greater direct governmental control. Milton R. Wessel, Science and Conscience, Columbia University Press, New York (1980).

8. Dr. Fredrickson, who approves of the location of RAC within NIH as the governmental body with clearest responsibilities in the field, has also praised the interagency group:

> In addition to maintaining a desirable amount of ecumenical spirit within the federal bureaucracy, [it] had the virtue of being there and ready for immediate convocation in the event one of the hypothetical hazards materialized and national resources needed to be mobilized and coordinated.

Supra note 4, at manuscript 9.

9. The experience of the Federal Interagency Committee is instructive. That committee was created as a result of Congressional pressure. It was very active during its first year, when it was responding to a mandate from the highest levels of the Executive Branch to review the nature and scope of recombinant DNA activities in the Federal and private sectors and to recommend appropriate responses in terms of guidelines, regulations, and/or legislation. Once this task was complete, the committee slowly slid into quiescence, not because DNA research no longer raised important issues, but because the member agencies (other than NIH) were not active in this field so the committee did not have much to "coordinate."

10. A two-year extension of the Commission is proposed in pending legislation, S.2311, the Biomedical Research, Training, and Medical Library Assistance Amendments of 1982.

11. Arthur Lubow, Playing God with DNA, 8 New Times 48, 64 (Jan. 7, 1977) (quoting Robert L. Sinsheimer).

APPENDIX A: GLOSSARY

Amino acids - The building blocks of proteins. There are 20 common amino acids; they are joined together in a strictly ordered "string" that determines the character of each protein.

Anneal - The process by which the complementary base pairs in the strands of DNA combine.

Bacteriophage (or phage) - A virus that multiplies in bacteria. Bacteriophage lambda is commonly used as a vector in recombinant DNA experiments.

Biotechnology - The collection of industrial processes that involve the use of biological systems. For some of these industries, these processes involve the use of genetically engineered microorganisms.

Cell fusion - The fusing together of two or more cells to become a single cell.

Chromosomes - The threadlike components of a cell nucleus that are composed of DNA and protein. They contain most of the cell's DNA.

Classical genetics - The body of knowledge that deals with the laws of inheritence of genes such as determined by appropriate test matings. (Compare molecular genetics.)

Clone - A group of genetically identical cells or organisms asexually descended from a common ancestor. All cells in the clone have the same genetic material and are exact copies of the original.

Conjugation - The one-way transfer of DNA between bacteria in cellular contact.

Crossing-over - A normal genetic event that always occurs during the reduction division of germ cell formation, which involves the breakage and reunion of DNA molecules.

Cut - A break that occurs in both strands of a DNA molecule opposite one another.

Cytoplasm - The protoplasm of a cell, external to the cell's nuclear membrane.

Diploid - A cell with the usual number of chromosomes, in contrast to haploid.

DNA (deoxyribonucleic acid) - The genetic material found in all living organisms. Every inherited characteristic has its origin somewhere in the code of each individual's complement of DNA.

DNA vector - A vehicle for transferring DNA from one cell to another.

Embryo - The early developmental stage of an organism produced from a fertilized egg.

Escherichia coli (*E. coli*) - A bacterium that commonly inhabits the human intestine. It is an organism used in many microbiological experiments.

Endonuclease - An enzyme that nicks or cuts DNA molecules; unlike a exonuclease, it does not require a free end to act. (*See also* restriction enzyme.)

Enzyme - A functional protein that catalyzes a chemical reaction. Enzymes control the rate of metabolic processes in an organism.

Eukaryote - A higher, compartmentalized cell characterized by its extensive internal structure and the presence of a nucleus containing the DNA. All multicellular organisms are eukaryotic. The simpler cells, the prokaryotes, have much less compartmentalization and internal structure; bacteria are prokaryotes.

Exonuclease - An enzyme that removes bases sequentially from the ends of a linear DNA molecule.

Fermentation - The biochemical process of converting a raw material such as glucose into a product such as ethanol.

Gamete - A mature reproductive cell.

Gene - The hereditary unit, such as a segment of DNA coding for a specific protein.

Gene expression - The manifestation of the genetic material of an organism as specific traits.

Gene mapping - Determining the relative locations of different genes on a given chromosome.

Genetic code - The biochemical basis of heredity consisting of codons (base triplets along the DNA sequence) that determine the specific amino acid sequence in proteins and that are the same for all forms of life studied so far.

Genetic drift - Changes of gene frequency in small populations due to chance preservation or extinction of particular genes.

Germ cell - The sex cell (sperm or egg). It differs from other cells in that it contains only half the usual number of chromosomes. Male and female germ cells fuse during fertilization.

Germ plasm - The total genetic variability available to an organism, represented by the pool of germ cells or seed.

Hybridoma - A rapidly proliferating cell made by fusing a myeloma cell with another cell. (Myeloma is a cancer of plasma cells.)

Haploid - A cell with half of the usual number of chromosomes.

Hormones - The "messenger" molecules of the body that help coordinate the actions of various tissues; they produce a specific effect on the activity of cells remote from their point of origin.

In vitro - Outside the living organism and in an artificial environment.

In vivo - Within the living organism.

Messenger RNA - Ribonucleic acid molecules that transmit the genetic information from the nucleus to the cytoplasm, where they guide protein synthesis.

Molecular genetics - Deals with the study of the nature and biochemisty of the genetic material. Includes the technologies of genetic engineering that involve the directed manipulation of the genetic material itself.

Monoclonal antibodies - Antibodies derived from a single source or clone of cells that recognize only one kind of antigen.

Mutation - Any change that alters the sequence of bases along the DNA, changing the genetic material.

Nick - A break in one strand of a DNA molecule in which no bases are removed.

Nucleic acid - A polymer composed of DNA or RNA subunits.

Nucleotides - The fundamental units of nucleic acids. They consist of one of the four bases—adenine, guanine, cytosine, and thymine (uracil in the case of RNA)--and its attached sugar-phosphate group.

Phage - (See bacteriophage.)

Plasmid - Hereditary material that is not part of a chromosome. Plasmids are circular and self-replicating. Because they are generally small and relatively simple, they are used in recombinant DNA experiments as acceptors of foreign DNA.

Polymorphism - A gene or unexpressed DNA variant that occurs in a population with a frequency too great to be explained by mutation.

Protein - A linear polymer of amino acids; proteins are the products of gene expression and are the functional and structural components of cells.

Recombinant DNA - The hybrid DNA produced by joining pieces of DNA from different sources.

Restriction enyzme - An enzyme within a bacterium that recognizes and degrades DNA from foreign organisms, thereby preserving the genetic integrity of the bacterium. In recombinant DNA experiments, restriction enyzmes are used as tiny biological "scissors" to slice foreign DNA before it is recombined with a vector. These enzymes are also called restriction endonucleases.

RNA (ribonucleic acid) - In its three forms--messenger RNA, transfer RNA, and ribosomal RNA—it assists in translating the genetic message of DNA into the finished protein.

"Shotgun" method - A technique for obtaining the desired gene that involves chopping up the entire genetic complement of a cell using restriction enzymes, then attaching each DNA fragment to a vector and transferring it into a bacterium, and finally screening the bacteria to locate those producing the desired product.

Somatic cell - One of the cells composing parts of the body (e.g., tissues, organs) other than a germ cell.

Totipotency - Capability of a cell, prior to differentiation, to express all of its genetic material.

Transduction - The process by which foreign DNA becomes incorporated into the genetic complement of the host cell.

Transformation - The transfer of genetic information by DNA separated from the cell.

Vector - A transmission agent; a DNA vector is a self-replicating DNA molecule that transfers a piece of DNA from one host to another.

Virus - An infectious agent that requires a host cell in order for it to replicate. It is composed of either RNA or DNA wrapped in a protein coat.

Zygote - A fertilized egg.

NATIONAL COUNCIL OF THE
CHURCHES OF CHRIST IN THE U.S.A.

THE WASHINGTON OFFICE
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M. William Howard, President Claire Randall, General Secretary

APPENDIX B

June 20, 1980

MESSAGE FROM THREE GENERAL SECRETARIES

We are rapidly moving into a new era of fundamental danger triggered by the rapid growth of genetic engineering. Albeit, there may be opportunity for doing good; the very term suggests the danger. Who shall determine how human good is best served when new life forms are being engineered? Who shall control genetic experimentation and its results which could have untold implications for human survival? Who will benefit and who will bear any adverse consequences, directly or indirectly?

These are not ordinary questions. These are moral, ethical, and religious questions. They deal with the fundamental nature of human life and the dignity and worth of the individual human being.

With the Supreme Court decision allowing patents on new forms of life — a purpose that could not have been imagined when patent laws were written — it is obvious that these laws must be reexamined. But the issue goes far beyond patents.

New life forms may have dramatic potential for improving human life, whether by curing diseases, correcting genetic difficiencies or swallowing oil slicks. They may also, however, have unforseen ramifications, and at times the cure may be worse than the original problem. New chemicals that ultimately prove to be lethal may be tightly controlled or banned, but we may not be able to "recall" a new life form. For unlike DDT or DES — both of which were in wide use before their tragic side effects were discovered — life forms reproduce and grow on their own and thus would be infinitely harder to contain.

Control of such life forms by any individual or group poses a potential threat to all of humanity. History has shown us that there will always be those who believe it appropriate to "correct" our mental and social structures by genetic means, so as to fit their vision of humanity. This becomes more dangerous when the basic tools to do so are finally at hand. Those who would play God will be tempted as never before.

We also know from experience that it would be naive and unfair to ask private corporations to suddenly abandon the profit motive when it comes to genetic engineering. Private corporations develop and sell new products to make money, whether those products are automobiles or new forms of life. Yet when the products are new life forms, with all the risks entailed, shouldn't there be broader criteria than profit for determining their use and distribution? Given all the responsibility to God and to our fellow human beings, do we have the right to let experimentation and ownership of new life forms move ahead without public regulation?

These issues must be explored, and they must be explored now. It is not enough for the commercial, scientific or medical communities alone to examine them; they must be examined by individuals and groups who represent the broader public interest. In the long-term interest of all humanity, our government must launch a thorough examination of the entire spectrum of issues involved in genetic engineering to determine before it is too late what oversight and controls are necessary.

We believe, after careful investigation that no government agency or committee is currently exercising adequate oversight or control, nor addressing the fundamental ethical questions in a major way. Therefore, we intend to request that President Carter provide a way for representatives of a broad spectrum of our society to consider these matters and advise the government on its necessary role.

We also intend to ask the appropriate Congressional Committees to begin immediately a process of reviewing our patent laws looking to revisions that are necessary to deal with the new questions related to patenting life forms. In addition, we will ask our government to collaborate with other governments with the appropriate international bodies, such as the UN, to evolve international guidelines related to genetic engineering.

Finally, we pledge our own efforts to examine the religious and ethical issues involved in genetic engineering. The religious community must and will address these fundamental questions in a more urgent and organized way.

Dr. Claire Randall, General Secretary
National Council of Churches

Rab. Bernard Mandelbaum, General Secretary
Synagogue Council of America

Bishop Thomas Kelly, General Secretary
United States Catholic Conference

APPENDIX C: FEDERAL GOVERNMENT INVOLVEMENT IN GENETIC ENGINEERING*

I. LABORATORY RESEARCH

Several agencies conduct or sponsor scientific research that either uses recombinant DNA molecules or studies the technique and its applications.

A. Department of Agriculture

The Department of Agriculture (USDA) funds several types of research involving genetic engineering in plants, animals, and microorganisms. Most research is in the following general categories: (1) studies of the normal genetic mechanisms of plants and animals (including the structure and function of nuclear, mitochondrial, and chloroplast genes, and the control of gene expression during development), with the goal of transferring functioning genes into higher organisms; (2) studies of viruses, bacteria, fungi, and other microbial agents that are pathogens or symbionts of plants, animals, or insects. The goal of the research is the eventual use of recognition sequences of microbes to introduce genes into higher organisms, extend the active range of nitrogen-fixing bacteria, or modify agents to achieve biological control of pathogenic microbes or insects; (3) studies to isolate and clone DNA sequences for useful proteins, and to gain the expression of these genes in bacteria in order to manufacture products, such as vaccines (*e.g.*, corn, soybean, wheat) and specific enzymes; and (4) studies to genetically engineer microbial organisms that will more efficiently produce useful fermentation products (e.g., fermented foods, antibiotics) or degrade certain compounds (e.g., industrial wastes, residual pesticides).

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* The information included in this appendix was provided by government officials as part of a survey conducted by the President's Commission in September 1980 and updated in August 1982.

B. Department of Defense

The interest of the Department of Defense (DOD) and its subordinate military departments in the use of genetic engineering technology is principally directed to the prevention of disease and the fielding of those devices and methodologies that will ensure the survival and continued effectiveness of military personnel in a toxic environment.

Current DOD programs using genetic engineering techniques include vaccines for dysentery, malaria, botulism, anthrax, hemorrhagic fevers (including Rift Valley and Dengue fevers), rickettsial diseases, and trypanosomiases--all items of significance to the medical protection of U.S. Forces. Studies continue on cloning the human gene for acetylcholinesterase and the receptor for acetylcholine (which will be applied in developing treatments for military personnel exposed to chemical warfare agents) and on cloning the squid gene for Diisopropylfluorophosphatase for organophosphorus detoxification. Further studies deal with the molecular basis of marine biofouling.

C. Department of Energy

Many of the Department of Energy's (DOE) investigators have used recombinant DNA techniques in their work. Genes are being cloned in order to obtain sufficient material to analyze the structure of genes, to deduce structure-function relationships, to analyze the molecular basis of mutation, and to obtain genetic material as probes for analysis. The genes come from a variety of sources, but the cloning is always done in microorganisms.

Continuing studies of a number of proteins are being expanded to include analysis of the structure of the genes involved. These include trytophan synthetase, metallothionein, rhodopsin, globin, and several enzymes involved in DNA repair processes. Studies are also under way to look at several aspects of cancer; these include cloning the genes for several liver enzymes that are turned off when cancer develops, cloning a naturally occurring mouse tumor virus, and developing cloning and isolation techniques to search for genes that occur only in tumor tissues.

In other projects, a gene from E. coli is being put in Chinese hamster cells to study the occurrence of mutations; an unusual form of DNA is being prepared by recombinant DNA techniques to study how it is repaired; and genes in corn are being cloned to understand genetic elements called transposons. In a collaborative project with the Centers for Communicable Diseases, fragments of DNA from a pathogenic organism are being cloned so probes can be developed to identify the organism in human tissues.

In projects related to biomass and fermentation, the genes for the multienzyme complex called cellulase are being cloned and analyzed, and an attempt is being made to introduce the enzyme xylose isomerase into certain kinds of yeast so they may ferment pentoses.

Future work being considered is along much the same line--examination of structure-function relationships of genes of particular interest, use of cloned genes to prepare hard-to-isolate gene products, and applied approaches as the needs and opportunities arise.

D. Environmental Protection Agency

The Office of Research and Development has undertaken a number of research studies and has represented the agency in various outside forums. Two assessments of the state of recombinant DNA usage in agricultural and industrial sectors and the impact of these applications on the environment have been commissioned. In addition, projects now in progress deal with events associated with environmental release of microbes. One study involves a computer simulation of the probability of escape of genomes from laboratories or commercial fermenters. Another is exploring survival of organisms in environmental media, and a third deals with the likelihood of genetical exchange of microbes in water and sewage. The office has participated with other groups and has established an institutional advisory group. Most recently, the staff initiated a seminar series designed to acquaint policymakers with environmental consequences of the technology, and they will participate in a research conference on the genetic control of environmental pollutants in 1983.

E. National Institutes of Health

The National Institutes of Health (NIH) is the major funder of basic research involving recombinant DNA techniques. It also supports several projects specifically designed for risk assessment. Both as a funding source and as part of its responsibilities for the protection of human research subjects, NIH will have a major role in clinical trials of gene therapy.

F. National Science Foundation

The National Science Foundation (NSF) funds several types of biological research involving recombinant DNA molecules: (1) gene regulation and expression; (2) structure and organization of chromosomes; (3) evolution and systematics; (4) organization and function of subcellular bodies; (5) transfer of genes including nitrogen-fixing genes to plants; and (6) development of recombinant DNA technology.

II. REGULATION

Several agencies have regulatory authority that extends to products of recombinant DNA technology.

A. Department of Agriculture

USDA has responsibilities for the inspection and certification of some products of recombinant DNA technology and the regulation of some organisms that may be used for recombinant DNA research. For example, USDA regulates importation into the United States of the foot-and-mouth virus that is used in vaccine research. Like other animal biological products, this vaccine would be licensed by the USDA.

USDA also establishes guidelines for the introduction and distribution of pathogenic microorganisms, other pests (insects, nematodes, noxious weeds), and plant germ plasm.

B. Environmental Protection Agency

In 1976, EPA's general counsel staff determined that some of the Federal statutes at EPA may apply to aspects of the bioengineering field. Their analysis included the Clean Air Act, Clean Water Act and Toxic Substances Control Act (TSCA) but did not address the other statutes under the Administrator.

Although several EPA statutes may apply, none has initiated a program to address biotechnology issues. Staff involved in administering the Federal Insecticide, Fungicide and Rodenticide Act and TSCA are currently reviewing the applied genetics field to consider the impact of the technology. The pesticide program has made the most progress, since it has already carried out registration reviews of over a dozen microbial agents that are used as pesticides. Generic testing guidelines are being readied for publication that will lay out the product chemistry, toxicology, environmental fate, and effects on nontarget species for testing for demonstration of safety in the registration process. The extent to which the guidelines may be altered to evaluate genetically engineered microbes as contrasted with naturally occurring agents has not been determined. Under TSCA, the Agency has broad authority over new and existing chemicals. The potential for TSCA to address the products of applied genetics as "new" chemicals is also being studied.

C. Federal Trade Commission

The Federal Trade Commission's (FTC) activities, which involve primarily enforcement actions, are concerned with the prevention and elimination of unfair business practices and restraint of trade. The Commission may exercise its enforcement powers to protect competition and consumers against practices that restrict research, development, production, or marketing of genetic technology and products or that might result in harm to consumers through unfair or deceptive advertising and marketing practices.

D. Department of Health and Human Services

1. Centers for Disease Control. The Centers for Disease Control (CDC) has responsibility for the interstate shipment of etiologic (*i.e.*, disease-inducing) agents and applies existing regulations (pertaining, for example, to volume and packaging) to DNA products identified as etiologic agents. (See also Department of Transportation below.) CDC

provides a 24-hour hotline for reports of leakage of any such agents during transport.

a. *Center for Infectious Diseases*. As part of its responsibility for disease diagnosis and prevention, this Center conducts epidemiological investigations and research on a broad range of infectious diseases of public health importance. Considerable emphasis is placed on studying the molecular biology of many pathogenic microorganisms, their epidemiology, disease-producing mechanisms, antibiotic-resistance profile, and the development of candidate vaccines. Some of the molecular biology research involves the use of recombinant DNA technology. Examples of such research are: (1) cloning pencillinase-producing plasmid fragments from *Neisseria gonorrhoeae* in *E. Coli* to test for mobilization properties, and cloning *N. gonorrhoeae* genes for studies of proline synthesis and to further the use of auxotyping as an epidemiologic tool; (2) cloning genes for cadmium resistance and penicillinase production, which appear to be linked in *Staphylococcus aureus* and *S. epidermidis*, to determine if *S. epidermidis* can serve as a reservoir for the penicillinase genes; (3) cloning of genes from influenza viruses, poliovirus, rabiesvirus, and and variola into bacteria to (a) study the structure and function of nucleic acids, (b) study viral pathogenesis, (c) develop molecular diagnostic procedures (i.e. hybridization tests to identify viral agents), (d) improve and develop technology for use in molecular epidemiology, and (e) develop techniques for rapid sequencing of those peptides identified as the key antigenic moiety for influenza strains of known or anticipated epidemic potential; (4) cloning of Venezuelan equine encephalitis (VEE) virus genome into bacteria to enable subsequent reconstuctions of the viral genome sequence, to identify those regions that code for antigenic glycoproteins responsible for inducing immunity, and to reconstruct synthetically the amino acids required for a vaccine.

b. National Institutes for Occupational Safety and Health (NIOSH). NIOSH has recently undertaken a program to help identify potential health hazards to workers involved in recombinant DNA work. Walk-through surveys were conducted at six companies. Assessments of the potential for worker exposure were made based on process design and operations. NIOSH has also developed, with other CDC experts, guidelines for medical surveillance of exposed workers. Finally, NIOSH is continuing research into the best available fermentation control technology, which would form the basis for future control in the use of recombinant organisms.

2. Food and Drug Administration. Products under the Food and Drug Administration's (FDA) regulatory jurisdiction produced using recombinant DNA methods are subject to the same regulatory standards as products derived from conventional technologies.

In general, it is expected that new applications for FDA approval will be required for products obtained via recombiant DNA technology that fall under the Agency's regulatory purview. For the first such products, which are currently under clinical investigation, the requirement for new applications is clear: human insulin has not previously been marketed; recombinant human growth hormone (hGH) is actually methionyl-hGH, an analogue of the (approved) natural substance; and some recombinant human interferon preparations may be chemically different from the interferons derived directly from human cell sources.

Moreover, despite substantial experience with products such as vaccines, antibiotics, and toxoids derived from natural components of microorganisms, there is little experience with substances produced by genetic manipulation of microorganisms. Moreover, some of the microorganisms that may be employed to produce recombinant products have not been previously employed to produce drugs or biologics for human use. Thus, the possibility of encountering novel toxicities is a concern.

In the future, it is expected that, where consistent with individual Bureau policy, new applications will be required for products obtained via recombinant DNA technology, even if identity is demonstrated with the natural substance, or with a previously approved substance produced in a conventional way. However, each case will be handled on an ad hoc basis because of the many different kinds of products expected. Data required to support such applications will vary widely and depend on a number of factors, including, but not limited to: whether the product is identical to a previously approved product; the projected length of time of use; the amount of previous experience with the product produced conventionally; and the amount of previous experience with recombinant DNA-derived substances.

3. National Institutes of Health. The National Institutes of Health (NIH), with its Recombinant DNA Advisory Committee, has established guidelines for the safe conduct of recombinant DNA research. The guidelines have been adopted by all Federal agencies and apply to all Federally funded research, with voluntary compliance by the private sector. As part of the voluntary compliance scheme, NIH reviews some private research. A limited number of recombinant DNA experiments must be reviewed and approved by NIH prior to initiation. Biosafety committees are required at institutions that conduct recombinant DNA research and that are registered with NIH.

E. Department of Labor

Occupational Safety and Health Administration

The Occupational Safety and Health Administration (OSHA) will continue to monitor activities in genetic engineering and collect information that might be used as a basis for a regulatory effort. OSHA has no immediate plans for regulatory activities in this area.

F. Department of Transportation

Etiologic agents are categorized as hazardous materials and are subject to DOT regulations issued under the Hazardous Materials Transportation Act (18 U.S.C. 1801 et seq.). These regulations are associated with CDC regulations and apply to the transport of recombinant DNA molecules that have been incorporated into any etiologic agent listed in the CDC regulations.

III. INFORMATION/EDUCATION

A. Department of Commerce

The National Bureau of Standards has not been involved thus far in any work involving recombinant DNA. It expects, however, to carry out some of its traditional roles, such as establishing equivalency of chemical products and developing test methods and reference standards for products developed by recombinant DNA methods. One example might be determining whether any feedstocks produced with recombinant DNA methods contain by-products not produced by traditional processes. The Bureau's focus is on physics, chemistry, and engineering.

Until the Supreme Court reached its decision on the patentability of living organisms in June 1980, the Patent and Trademark Office (PTO) had deferred the processing of the more than 100 patent applications involving products of genetic engineering. The PTO has now taken some form of action on all these applications, applying the usual standards of patentability. Patent applications involving use of recombinant DNA techniques or related technology were being received at the estimated rate of 10-15 per month in mid-1982.

The Department of Commerce is also interested in the protection of trade secrets, should private companies come under Federal regulation.

B. Department of State

The Department of State's involvement in genetic engineering, recombinant DNA and related technology emanates from its broad mandate to pursue U.S. foreign policy objectives, and its specific statutory responsibility for coordinating U.S. scientific and technological collaboration with other nations. Foreign policy concerns of relevance to genetic engineering include: international trade and commerce, particularly elimination of existing or potential nontariff trade barriers and the protection of patent rights; national security aspects of technology transfer; and environmental health and safety.

Although the Department of State does not directly sponsor or carry out research or development in this field, it obtains and provides information on policies and programs of other nations to support the R&D efforts of U.S. public and private institutions. The Department also coordinates U.S. participation in a broadening array of international organizations active in genetic engineering in an effort to influence the character of these efforts and to maximize their benefits. Such organizations include the World Health Organization, the UN Environment Program, the Economic Commission for Europe, and the Organization for Economic Cooperation and

Development (OECD), as well as international nongovernmental bodies such as the International Council of Scientific Unions (ICSU).

C. National Academy of Sciences

The National Academy of Sciences (NAS) has not undertaken any activities focusing on the ethics of human applications of genetic technology. However, it has sponsored a Workshop of Priorities in Biotechnology Research for International Development. In addition, on May 20, 1982, a meeting was held of an ad hoc Committee on New Separation Processes for Genetic Engineering and Chemical and Energy Industries. A major focus of this meeting was on applications of biotechnology to separation processes, *e.g.*, removal of toxic or valuable contaminants from liquid phases. The meeting was convened by NAS's Commission on Engineering and Technical Systems.

D. National Institutes of Health

In 1976 the Federal Interagency Committee on Recombinant DNA Research was formed under NIH auspices. It had three responsibilities: (1) review the nature and scope of DNA activities in the Federal and private sector; (2) determine the feasibility of extending NIH guidelines to all sectors; and (3) recommend legislative or executive action concerning these guidelines. The group met until 1980 at which time an Industrial Practices Subcommittee was formed. The full Committee recommended that legislation be passed extending NIH's recombinant DNA guidelines to the private sector, but Congress failed to pass the measure. Neither the full Interagency Committee nor its Industrial Practices Subcommittee is currently active.

E. National Science Foundation

1. Law and Social Sciences Program. This program supports a research project entitled "New Regulatory Forms: Recombinant DNA Research," which is carried out by Anselm Strauss at the University of California, San Francisco. As changes in science and technology have raised questions directly related to broader social, economic, political, and ethical issues, new law has been developed, requiring new patterns of regulation. This project specifically addresses issues of the scope of regulation, the role for technical specialists, and the criteria and standards applied by regulatory agencies and courts in terms of the history of regulation of DNA research. The study focuses on the relationships among interested parties in the regulatory arena, with attention to who those participants are and the "social worlds" they represent (the occupational settings in which they operate) and how they represent them. Emphasis is given to the strategy and tactics of conflict and negotiation among those parties. A manuscript describing this study is expected to be completed in early 1983.

2. Ethics and Values in Science and Technology. The program on Ethics and Values in Science and Technology (EVIST) supports research that shows promise of contributing to professional and public understanding of the ethical and value implications of genetic engineering. The program has supported the work of Charles Weiner, at MIT, to develop a historical archive of public and professional controversies surrounding recombinant DNA research and development. In September 1981 the NSF also awarded a grant to Clifford Grobstein, at the University of California, San Diego, to conduct a technology assessment of potential human applications of

recent advances in genetics. Monographs are in preparation describing studies by Sheldon Krimsky at Tufts University on a social history of the recombinant DNA controversy and by a team of researchers headed by Diana Dutton at Stanford University concerning the roles of public participation in controversies surrounding medical innovations, including a discussion of recombinant DNA.

F. Office of Technology Assessment, U.S. Congress

The Office of Technology Assessment has undertaken three studies in the field of genetics:

Impacts of Applied Genetics: Micro-organisms, Plants and Animals. This report, released in April 1981, describes current and potential applications of classic and molecular genetic technologies to produce substances in three major industrial sectors--pharmaceuticals, chemicals, and food. Three applications involving release of genetically altered organisms to the environment are discussed: mineral leaching and recovery, enhanced oil recovery, and pollution control. Current and potential applications to higher plants and animals are described. Other parts of the report address the problems of assessing the risk of genetic engineering, the regulation of the technology, the patenting of life forms, and various science/society issues raised by the new genetic techniques. Policy options for Congressional consideration are described as well as the pros, cons, and consequences associated with them.

Genetic Screening and Cytogenetic Surveillance in the Workplace. This assessment examines the state of the art of genetic screening and cytogenetic surveillance as means of identifying individuals at high risk for particular chemicals in the workplace or environments where the entire workforce may be at risk. It examines legal issues raised by genetic testing in the workplace, applicable ethical principles, and economic considerations. A survey of genetic testing in the workplace was conducted as part of the study, which is due to be completed in the fall of 1982.

A Comparative Assessment of the Commercial Development of Biotechnology. This assessment examines whether biotechnology (which includes recombinant DNA, cell fusion, fermentation, and enzyme technology) is developing in the United States in a way that will leave the nation in a competitive position with other nations in the years ahead. Besides describing the state of the art here and in other countries, major influences likely to affect future development of the industry are reviewed. These include government policies on research funding, patents, health and safety regulations, antitrust laws, and taxation as well as industrial-academic relationships and their influence on funding, research, manpower, training, and information flow. The study is due to be completed in the summer of 1983.

APPENDIX D

I. Commission Hearings

September 16, 1980

Techniques and Problems

Dr. Gilbert S. Omenn, Associate Director for Human Resources, Veterans, and Labor, Office of Management and Budget, Executive Office of the President

Richard Roblin, Ph.D., Cancer Biology Program, Frederick Cancer Research Center, Frederick, Maryland

Conceptual Issues

Richard Hull, Ph.D., Associate Professor of Philosophy, State University of New York, Buffalo

Federal Activity

William Gartland, Director, Office of Recombinant DNA Activities, National Institutes of Health

Michael Lambert, Professional Assistant, Technology Assessment and Risk Analysis, National Science Foundation

. Joshua Menkes, Technology Assessment and Risk Analysis Group, National Science Foundation

Arthur Norberg, Program Manager, Ethics and Values in Science and Technology, National Science Foundation

Dr. Joseph Perpich, Executive Secretary, Federal Interagency Advisory Committee on Recombinant DNA Research, National Institutes of Health

Dr. Bernard Talbot, Executive Secretary, Industrial Practices Subcommittee, National Institutes of Health

July 10, 1982

Panel Discussion of Draft Report

Dr. French Anderson, Chief, Laboratory of Molecular Hematology, National Heart, Lung, and Blood Institute, National Institutes of Health

Nicholas Wade, Editorial Board, New York Times and author of The Ultimate Experiment: Man-Made Evolution

Public Comment

J. Robert Nelson, Professor of Theology, Boston University

II. Advisors to the Commission

A. Special Consultant: Tabitha M. Powledge, M.S.

B. Consultant Panel

David Baltimore, Ph.D., Professor of Microbiology, Massachusetts Institute of Technology
Peter Day, Ph.D., Director, Plant Breeding Institute, Trumpington, Cambridge, England
Troy Duster, Director, Institute for the Study of Social Change, University of California, Berkeley
Zsolt Harsanyi, Ph.D., Office of Technology Assessment, U.S. Congress
Ruth Hubbard, Ph.D., Harvard Biological Laboratories, Harvard University
Peter Barton Hutt, Esq., Covington & Burling, Washington, D.C.
David Jackson, M.D., Genex Laboratories, Rockville, Maryland
Yuet Wai Kan, M.D., School of Medicine, University of California, San Francisco
Leon Kass, Henry R. Luce Professor of the Liberal Arts of Human Biology, University of Chicago
Sheldon Krimsky, Department of Urban and Environmental Policy, Tufts University
Eleanor Nightingale, Ph.D., Institute of Medicine, National Academy of Sciences
Christine Oliver, Ph.D., Oil, Chemical and Atomic Workers International Union, Watertown, Massachusetts
Richard Roblin, Ph.D., Frederick Cancer Research Center, Frederick, Maryland
Frank Ruddle, Chairman, Department of Biology, Yale University
Michael Shapiro, Law Center, University of Southern California
Margery Shaw, Ph.D., Professor of Medical Genetics, Graduate School of Biomedical Sciences, University of Texas
Maxine Singer, M.D., Chief, Laboratory of Biochemistry, National Cancer Institute,
Marc Skolnick, M.D., College of Medicine, University of Utah
Stephen Stitch, Professor of Philosophy, University of Maryland
Leroy Walters, Ph.D., Director, Kennedy Institute for Bioethics, Georgetown University

C. Additional Advisors from Federal Agencies (1981)

Dr. French Anderson, Chief, Laboratory of Molecular Hematology, National Heart, Lung, and Blood Institute, National Institutes of Health
John Fletcher, Ph.D., Assistant for Bioethics to the Director, Warren G. Magnuson Clinical Center, National Institutes of Health
William Gartland, Director, Office of Recombinant DNA Activities, National Institutes of Health
Gretchen Kolsrud, Ph.D., Program Manager, Genetics and Population Program, Office of Technology Assessment, U.S. Congress
Arthur Norberg, Program Manager, Ethics and Values in Science and Technology, National Science Foundation
Joseph Schulman, Ph.D., M.D., Head, Human Biochemical and Developmental Genetics Section, National Institute of Child Health and Human Development
r. Bernard Talbot, Executive Secretary, Industrial Practices Subcommittee, National Institutes of Health

D. Theological Consultants

Representatives of Religious Organizations

John R. Connery, S.J., for the U.S. Catholic Conference
J. Robert Nelson, for the National Council of Churches
Seymour Siegel, D.H.L., for the Synagogue Council of America

Commentators

Robert A. Brungs, S.J., Director, Institute for Theological Encounter with Science and Technology, St. Louis, Missouri
James F. Childress, Professor of Religious Studies, University of Virginia
Charles E. Curran, S.T.D., Professor of Moral Theology, Department of Theology, School of Religious Studies, Catholic University
Sister Margaret A. Farley, Associate Professor of Ethics, Yale Divinity School
Dr. James M. Gustafson, Professor of Theological Ethics, Divinity School, University of chicago
Karen Lebacqz, Ph.D., Associate Professor of Christian Ethics, Pacific School of Religion, Berkeley, California
The Rev. Donald G. McCarthy, Ph.D., Director of Education, Pope John XXIII Medical-Moral Research and Education Center, St. Louis, Missouri
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Harmon L. Smith, Professor of Moral Theology and of Community and Family Medicine, Duke University
Gabriel Vahanian, Ph.D., Professor of Religion, Syracuse University

Mr. CAPRON. Thank you very much.

The Commission's study, like your committee's hearings over the next 3 days, focused on one particular and very important aspect of scientists' newly gained ability to manipulate the material that is responsible for the different forms of life on Earth. The Commission has been centrally concerned with the social and ethical implications of applying gene splicing—as this technique is known—directly to human beings.

The Commission began its study in September 1980, in response to the request of the President's science adviser. Urgent concern had been expressed to the President earlier that year by the Nation's three major religious associations that no governmental body was exercising adequate oversight or control, nor addressing the fundamental ethical questions.

In some ways, the Commission has found this concern to be well-founded. The Recombinant DNA Advisory Committee, known as RAC, at the National Institutes of Health has issued guidelines for Government-sponsored laboratory research with gene splicing, and researchers in privately sponsored labs and industrial concerns have affirmed their adherence to these standards; agencies with regulatory responsibilities are either dealing with gene splicing, such as the FDA's recent approval of human insulin produced in this fashion, or are at least preparing to do so. Yet none of these agencies has focused particularly on the direct human use of gene splicing nor upon the ethical questions.

These questions have been addressed, although certainly not resolved, by the Commission. In sharing some of our thinking with you today, I want to emphasize that the Commission sees its major contribution as sorting out some of the issues and stimulating thoughtful discussion of them over the long term. We have no intention of truncating such discussion with what would, of necessity, be premature conclusions for a field that is unfolding rapidly and in ways that cannot be precisely foretold.

I think it would be accurate, however, to say that while we have found that the religious leaders were correct in perceiving a lack of governmental oversight, we have not found in the gene splicing now being planned or undertaken the "fundamental danger" to human values, social norms or ethical principles that alarmed them.

THE ORIGINS OF CONCERN

The public's attention was first drawn to implications of genetic engineering by the actions of scientists concerned about the safety of their laboratory research with microorganisms. Although the initial public and scientific debate was focused on laboratory hazards, it became apparent that the implications of gene splicing were more far-reaching. Indeed, in some ways the success of laboratory experiments—which lead toward the use of gene splicing in industrial settings, in the general environment and in medical treatment—only heightens those anxieties.

In reviewing statements about gene splicing in the popular press, I have been struck by the frequent invocation of what Willard Gaylin some years ago called "the Frankenstein factor." The analogy is illuminating for several reasons.

First, Dr. Frankenstein was a creator of new life and the gene splicers have raised questions about mankind's role as creator.

Second, Dr. Frankenstein's creation was a frightening monster and gene splicing has raised fears about strange new life forms. These have often been expressed in terms of interfering with evolution. Some scientists have been concerned about the hazards created when the barriers against transfer of genetic material between species are breached. One of the results of research in this field, however, has been new understanding of the ways in which genetic material moves about within and between cells, meaning that some of the evolutionary barriers are less rigid than they were once thought to be.

The Frankenstein story also reminds us of the tale of "The Sorcerer's Apprentice"; in both, a development intended to be beneficial proved to be dangerous when it got out of control. Likewise in gene splicing, as Erwin Chargaff, a biochemist who has been particularly criticial of the field, has remarked, "You can stop splitting the atom, you can stop visiting the moon, you can stop using aerosols, but you cannot recall a new form of life."

The Frankenstein analogy also comes to mind because of people's concern that something is being done to them and their world by individuals concerned with their own goals but not necessarily with human betterment. As C. S. Lewis once observed, "Man's power over nature is really the power of some men over others with nature as their instrument."

But most particularly, it seems to me that the Frankenstein story was on the lips of many people, both scientists and lay people, because it dealt with the creation of a new being with a human form. Ultimately, the concerns about laboratory risks are not enough to explain the public or the scientific fascination with this topic. There are certainly other forms of research that pose comparable danger that have never excited as much public discussion. In the end, it is the potential human uses of the technique that are on people's minds.

THE BASIS OF GENE SPLICING

Before discussing the issues raised by the field, it might be helpful for me to say a few words about techniques and their uses. I'm sure that subsequent witnesses will provide you with greater detail on these and related subjects.

Perhaps I could use the blackboard just to leave you with a listing.

I should mention in passing that the commission did not include within its definition of genetic engineering several techniques which we really think are examples of reproductive technology—in vitro fertizilization and cloning. These are often mentioned in the same breath in the popular accounts. But really, what is involved there does not involve a necesssary manipulation of genetic material, although for certain of the therapeutic uses of genetic engineering it might well be necessary to have made progress in these reproductive areas.

Let me summarize what I have to say on the technical side, the three categories of gene splicing, as they may enter into the treatment of human beings.

I think it is important to be somewhat clear about the limited nature of the use of genetic engineering, or gene splicing in human beings, because one has the sense from some of the coverage, particularly from the popular impression, that something very radical is being talked about in the short run, which is not the case.

Nonetheless, I think that we should not dismiss public concerns about this. Last year the National Science Foundation published the results of its biennial public opinion survey on science, and genetic manipulation was the only area in which a majority of people, indeed almost two-thirds of the public, indicated that they were concerned that this work did not go ahead. So I think we are dealing with something in which the public concern remains very high, and we should try to be clear about what is going on.

I had the sense in reading some of the documents that came to us, and indeed even in looking at the churches' concern, that they thought perhaps scientists were going to be dipping down into some great genetic soup and lifting up the genes to create entirely new beings. One even had the image that was repeated in some of the popular press of the "Flying Nun," or something. You bring together human beings and birds and come up with a hybrid of that sort. That is not what we are talking about. (See fig. 1.)

Figure 1

HUMAN USES OF GENE SPLICING

I. Production of Drugs and Biologics

  A. Hormones, enzymes, etc. (such as insulin, interferon, and human growth hormone)

  B. Vaccines and antibodies

II. Genetic Screening and Diagnosis

  A. Carrier screening

  B. Presymptomatic diagnosis

  C. Prenatal diagnosis

  D. "Mapping" of human genes

III. Genetic Cure

  A. Cells Affected

    1. Somatic cells
    2. Germ-line cells

  B. Type of Treatment

    1. Gene therapy (addition of "normal" gene)
    2. Gene surgery (deletion or suppression of "abnormal" and addition of "normal" gene)

What we are talking about in the short run is simply the production either of drugs and biologics, like vaccines, or the production of antibodies through cell fusion techniques. As I mentioned already, the FDA has given approval to human as well as animal products that have come up through genetic engineering.

The second area is through genetic screening and diagnosis. And here too we are talking about something which has taken place already. Through the use of the restriction enzymes, which are really the tool that makes all of recombinant DNA research and development possible, scientists can cut lengths of the DNA in ways which should have a characteristic length, and the fragments that are cut can then be measured through a technique called electrophoresis. If there is a genetic mutation so that one of the expected nucleotides—that is, one of the chemicals that is responsible for the whole genetic code—has been changed, the break will not come at the right place. And there are several ways, which I won't go into now since other witnesses I am sure will, in which this can be done, either by looking for what is called a linked marker gene, or in some cases, as has been found with sickle cell, if the mutation occurs at the restriction site, which is right on the gene, then one can actually find the change in the gene itself.

This is a very powerful tool of diagnosis because in certain genetic diseases present screening methods require that the cells be cultured and that their biological product be measured biochemically. This new method does not look to the product, it looks directly to the gene.

The implication of this, of course, is that one would not be limited to looking for known genetic defects that have certain consequences, measurable consequences, but one could also look directly for any gene. That is still in the future for me. Thus far it has only been done in a limited number of diseases. Certainly that is one path that is open.

The area that was of most concern to the commission was neither of these two human uses of genetic engineering, but what might be called a genetic cure. This could take the form of treatment either of somatic cells or the treatment of germ-line cells. Several different names have been used to describe the techniques of treatment.

Some people describe something called gene therapy, where the intention is to place into the nucleus of the cell the gene that would correctly program the cell to produce a protein that the cell cannot now produce, which causes the genetic defect.

A refinement of that technique, which is sometimes described as gene surgery, would involve excising or suppressing the present gene, the defective gene that is turning out a gene product that is in some ways harmful to the individual. This technique would be a refinement in that it would eliminate that defective gene product that may be harmful, and that may in effect be fighting with the new useful gene product. Depending upon the type of genetic disease one is talking about, that change might be important.

Mr. GORE. Now, under gene cure, the differences between gene therapy or genetic engineering on somatic cells and germ-line cells is that with somatic cells, only the individual treated is affected, but with germ-line cells, whatever is done is passed on to future generations?

Mr. CAPRON. That is right.

Since none of this has been done successfully yet at all——

Mr. GORE. Well, both have been done in animals, right?

Mr. CAPRON. The change has been performed in animals, yes. There have now been the experiments in fruit flies that have shown it is possible to have the change occur in a way that corrects a genetic defect, and that would be passed on to subsequent generations, and experiments in mice have also been done that allow the inheritance to be expressed.

The significance of the research with the fruit flies is that in that case the gene was incorporated in a way that actually corrected the defect, and that is, of course, the goal of genetic engineering—not simply with human beings—not simply to get the gene into a cell, but to have it express itself in the gene product, and to replace whatever it is that is now causing the genetic disease.

The difference between somatic and germ-line, in the view of the witnesses who came before the commission and of the commission members, is important. I will try in talking about some of the issues to explain why we think there is some importance to this distinction.

One should note that the germ-line changes could come about in one of two ways. First, such changes might occur if the form of genetic therapy that was being used was one which had to be introduced systemwide because there was no way to remove the particular organ that was involved. The work on the blood disorders can be done, or it is hypothesized it could be done, by removing the bone marrow cells, treating them, and putting them back. But certain other diseases could not be treated this way because there would be no organ that could be removed, and one would have to find a way to get the genetic material into the body and try to target it for the cells you want. There is always the chance, and scientists will disagree as to how great that risk would be, and it would depend upon the design of the experiment, that the effect would not be limited to those cells, but could also affect the germline cells.

Second, another form of treatment, sometimes called zygote therapy, would involve an alteration at a very early stage of development, using the in vitro technology of having to culture the human organism and treat the cells because one is talking about a disease, say like cystic fibrosis, that affects so many organs of the body, and if the alteration is not made at the embryonic stage, certain irreversible changes will begin to take place. Thus, it would be desirable to have the genetic change occur early. Among the cells that would be affected would be those that are going to go on and create the next generation. So that certain kinds of changes, not accidentally but intentionally, would have to involve germinal changes.

Mr. GORE. And that would be done at an early stage in cell differentiation so as to affect all of the later cells?

Mr. CAPRON. Yes.

Mr. GORE. Now, isn't it true that scientists have already put human genes into animals?

Mr. CAPRON. Yes, in microorganisms. In fact——

Mr. GORE. And have them thrive successfully there?

Mr. CAPRON. Have them thrive?

Mr. GORE. Have them express themselves?

Mr. CAPRON. Yes.

Mr. GORE. Create effects in the animal.

All right. Go ahead.

Mr. CAPRON. The commission, in trying to understand people's anxieties about genetic engineering, looked to a number of issues. Perhaps it would be helpful if I reviewd those issues very briefly for you.

ISSUES OF MEANS

The first is the question of forbidden knowledge. In the view of Robert Sinsheimer, a leading biologist at Cal-Tech: "We must face the fact that there can be unwanted knowledge." It is true that the potential understanding of the machinery of life is an awesome prospect. Like the new knowledge associated with Copernicus, Darwin, Freud, and Einstein, that associated with the gene splicers offers further challenge to human beings' conception of themselves as the unique and even sacrosanct center of the universe. By identifying DNA and learning how to manipulate it, science seems to have reduced people to a set of malleable molecules that can be interchanged with those of species that people regard as inferior. Yet, as disorienting and perhaps even disruptive as the new knowledge may be, the commission rejects the idea that it should be regarded as forbidden.

Yet, unlike the earlier revolutionary discoveries, those in molecular biology are not merely descriptive, they give scientists vast new power for action. The use of these new powers has frequently been labeled "playing God." This description carries with it an implication that it is wrong for human beings to engage in this activity at all, that we have overreached ourselves by pretending to have God-like powers.

This objection, that in creating new life forms scientists are abusing their knowledge by interfering with nature, has several possible meanings. At least one is not persuasive. For milennia, people have interfered with nature both intentionally, through the breeding of new varieties of plants and animals, and unintentionally as a side effect of other human activities, including medicine itself.

There is some difference in aspects of gene splicing, however, that might create hybrids that are capable of reproducing themselves, but here the concern would not be that crossing species lines is inherently wrong, merely that if the effects are deleterious their harm may be multiplied by their perpetuation into later generations—a recombinant DNA Dutch elm disease, as it were. This is an issue that deserves to be treated with great care, but it is not one that raises a problem of principle.

There is, however, another aspect to the complaint about "playing God" in crossing species lines where a prohibition may be in order, and that is in the hybridization of human beings with other living things. Present research is entirely at the cellular level, such as the fusion of human cells with those of mice, or through the insertion of a single human gene, such as the gene for insulin production, into a microorganism.

The prospect of creating an actual being with partially human characteristics offends a deeply held taboo. There is, however, at the moment no legal or regulatory prohibition of such a step. And if the barrier is to survive in the face of scientific advances, the reasoning behind it will need further attention. It may, for example, be fruitful to clarify what it is about human beings that is unique, whether it is the sum of their characteristics or the possession of particular characteristics. There is a certain irony here since a person approaching the subject from a religious or philosophical position is likely to deny that human beings are simply a reflection of the particular chemicals that make them up, and yet the objection being raised is to an alternation in those chemicals.

ISSUES OF CONSEQUENCES

When one moves from absolute prohibitions on the human uses of gene splicing to questions of particular consequences, one is faced immediately with a realization of the great uncertainty in this field. The uncertainty is more than a question of whether a particular event will occur but also encompasses the ethical uncertainty that follows from not knowing whether a use of technology should be regarded as beneficial or harmful and even the conceptual uncertainty that comes from new developments that challenge people's fundamental beliefs. Let me highlight some of these issues very quickly for you.

There is first the concern for personal health. This concern has several bases—for example, the notion that in replacing a particular DNA sequence that is regarded as deleterious, a physician might also unintentionally be removing other genetic material that is in fact beneficial. To deal with them, IRB's at research institutions will need to be able to draw on the expertise of people knowledgeable about human genetics and particularly about gene splicing.

Second are questions of inheritance. The possibility that genetic changes would be inherited raises many questions. For example, would such alternations be so widespread in society that the "gene pool" would lose desirable diversity, thereby exposing mankind—like some inbred strain of rice or corn—to the risk of decimation by a newly arising pathogen. Although this concern is not yet pressing, decisions made now about gene splicing may affect society's ability to respond to this issue when it becomes a scientific possibility.

Beyond any physical consequences for future generations, the ability to change one's genes challenges the basic assumptions about people's links to, and responsibility for, their progeny. In some ways, one's responsibility may be increased—will it be acceptable for people simply to accept the results of the natural lottery by which characteristics are now determined or will "responsible parents" be expected to "correct" bad genes and to augment others to give their children an opportunity for a higher level of physical or cognitive functioning?

On the other hand, knowing that future generations may employ an even more advanced technlogy to alter or to replace characteristics passed on to them may weaken people's sense of genetic continuity. Furthermore, by blurring the line between what counts as a serious defect or disability and what is "normal functioning," gene splicing may alter our perception of what society owes to children, particularly those burdened by handicaps.

The potential of gene therapy or surgery to improve functioning calls into question the scope and limits of a central element of democratic political theory: the commitment to equality to opportunity. If genetic engineering became mandatory—along, perhaps, with restrictions on "natural reproduction"—in order to avoid the effects of the "natural lottery," what influence will that have on our opportunities for life?

Any discussion of equality leads naturally into a discussion of justice. Who should decide which lines of genetic engineering ought to be pursued and which applications of the technology to which patients ought to be undertaken? This is a question that seldom arises about medical progress. Decisionmaking in medicine is widely dispersed, resting upon the tripod of peer standards, patient consent and very broad and general State regulation—although this third leg of the tripod is receiving greater attention because of the extensive involvement of the State with the financing of medical care. But if genetic engineering comes to be seen as a very beneficial and powerful form of treatment, questions will certainly be raised about access to it not only in the use of techniques that have been developed but also in deciding about which areas need to be pursued.

It seems to me that this issue lies behind the concerns that have been expressed by many about the effect of commercial involvement in the basic research carried on by academic and other independent institutions and about the effects of such control on the availability of dispassionate expert advice for policymakers.

ISSUES OF CONCEPTS

Several of the other issues addressed by the President's Commission remain very diffuse although they are regarded as matters of importance. First, there are the questions raised about the effects of gene splicing on our sense of personal identity. The current tendency is to think of a person as an individual of a certain character and personality that is relatively fixed within certain boundaries.

But this concept—and the sense of predictability and stability in interpersonal relations that it confers—could quickly become outmoded if people are able to use gene splicing to make basic changes in themselves over the course of a lifetime. Of course, existing forms of medical treatment—particularly in the psychological and psychosurgical fields—can make profound changes in people. The sense there, however, is that of restoring a person to the self from which a disorder has caused him or her to deviate, not of creating a "new person," as is potentially—and I emphasize "potentially" at the moment—the case with gene splicing. Of course, the prospect for gene splicing of this sort is very remote, since the aspects of a person in question appear to be caused by a complex interaction of numerous genetic and environmental factors. The issue, however, is important enough to receive further attention.

Similarly, a question arises about the alteration of the genetic basis for the natural characteristics of all persons—that is, a change in "human nature." Basically, gene splitting of this sort would raise many of the same concerns I mentioned earlier regarding the hybridizing of a human being with another species. Yet this development seems like science fiction, since changes may be introduced more gradually as the ability is gained to change particular characteristics one by one.

At what point, and regarding which human qualities, would one say that a change in human nature has been made and how would one know whether such a change is desirable? You may recall the famous geneticist of an earlier generation, Herman Mueller, who advocated the use of selective breeding, a technique which would have required much more extensive social controls, for exactly this purpose. And he saw us achieving a more desirable form of human nature, perhaps more cooperative and the like.

It is interesting how variable one's definition of what is desirable is. It has been pointed out when Mueller first published his list, among the people who he cited as exhibiting good qualities was Lenin. During the cold war, when he published another version of the list, Lenin no longer appeared on it.

Obviously this is not yet a pressing issue—particularly when compared with the use of other techniques of indoctrination and behavior control that are already available to make some people act in ways that many would think go against human nature. Yet, it is worthwhile remembering in this and other contexts that developments in the field of gene splicing have come along more quickly than many had predicted. Therefore, one cannot assume that the day will never come when scientists will be capable of deliberate, selective and rapid alterations in the genetic basis of what is distinctly human.

ATTITUDE TOWARD THE ISSUES

Although the Commission has found that the issues raised by gene splicing in human beings can better be taken into account by biomedical scientists, Government officials, and the public if they are considered individually, it would be a mistake to respond to the new technology solely by reducing all concerns to assessments of particular consequences or applications.

Even after the potential consequences have been carefully sifted and their implications for human welfare have been explored, there remains an important residual concern expressed by the warning against playing God. It not only reminds human beings that they are only human and will someday have to pay if they underestimate their own ignorance and fallability, but it also points to the weighty and unusual nature of this activity, which stirs elusive fears that are not easily calmed.

At this point in the development of genetic engineering no reasons have been found for abandoning the entire enterprise—indeed, it would probably be naive to assume that it could be. To expect humanity to turn its back on what may be one of the greatest technological revolutions may itself betray a failure to recognize the limits of individual and social self-restraint.

Assuming that research will continue somewhere, it seems more prudent to encourage its development and control under the sophisticated and responsive regulatory arrangements of this country, subject to the scrutiny of a free press and within the general framework of democratic institutions. Efficient regulation and oversight will require considerable division of responsibility among different bodies and agencies. Legal controls will necessarily focus on the prevention of tangible harms to individuals and the environment.

Nonetheless, the Commission believes it is crucial that those entrusted with such oversight and regulation do not lose sight of the more elusive, but equally important, concerns about the human significance of genetic engineering or neglect such concerns because they do not fit neatly into existing institutional jurisdictions.

MECHANISMS FOR OVERSIGHT

In light of the important issues to which the Commission has given preliminary examination, it seems reasonable to seek to find one or a number of means of continuing oversight in this field. Unlike the situation 8 years ago, however, when the risks seen in the initial research with gene splicing lead to the imposition of a voluntary moratorium of certain lines of research, the creation of the RAC, and the issuance of Government regulations, there is no need for a sense of panic. It is the profound and fundamental nature of the issues at stake and not their immediacy that counsels the creation of appropriate means of oversight.

In looking to this future, the Commission reached several conclusions about the design of any oversight group. Briefly, they are, first, that the group should regard education as a prime objective. Second, that it should have a role of leadership as well as oversight within the Federal Government—meaning that it should, at a minimum, have action-forcing power. Third, it should have a diverse membership and ought to conduct its work in public.

Fourth, it should have means of drawing on disinterested expertise on a wide variety of scientific and technical issues. Fifth, it should treat in an unified framework all the issues raised by genetic engineering—including industrial as well as laboratory safety, environment hazards, agricultural and commercial opportunities and pitfalls, international ramifications, biomedical effects and risks, and social and ethical implications. Sixth, insofar as possible, its oversight functions should be separated from any sponsoring functions so that no conflict of interest will arise of the sort that plagued the old AEC. As a practical matter, the Commission saw great value in building on the history, largely regarded as successful, of RAC.

Mr. GORE. When you say RAC, some of our guests may not be familiar with that.

Mr. CAPRON. It is the Recombinant DNA Advisory Committee at the National Institutes of Health, set up in October of 1974. Donald Frederickson, who was associated when he was Director of NIH with its development, recently suggested that since it had already gone through two generations—first a largely scientific and technical body, and second, a more broadly based body concerned with laboratory hazards—perhaps the time had now come for a third generation RAC.

Rather than recommending a particular form of oversight, the Commission has put forward several suggestions as starting points for the discussion in Congress and by the President and the executive branch.

One means of supplementing a perhaps less active RAC would be through a mixed public-private body in the private sector such as those that have operated in other areas.

Alternatively, if it is felt that the extent of the Federal responsibility is so great, both in terms of safety issues and the promotion of the field, then a governmental body of greater breadth than the present RAC may be needed. The Inter-Agency Committee was established in 1974, and which has been inactive for the past several years, could be reinvigorated. This would have the advantage of direct involvement of the leading Federal agencies, but the disadvantage that its membership is entirely governmental and its meetings are not subject to the Federal Advisory Committees Act.

Another format would be the creation of a Genetic Engineering Commission, GEC, of 11 to 15 members from outside the Government, which could meet regularly to deal solely with this field. This group could have a majority of nonscientists, with the ability to draw on a series of technical panels to provide expertise not only in laboratory, agriculture, manufacturing and medical areas but also matters involving international controls.

In order to coordinate with the Federal agencies, it could draw on a panel of liaison officers from the Departments of Agriculture, Commerce, Defense, Energy, Health and Human Services, Interior, Labor and State as well as the National Science Foundation, the National Endowment for the Humanities, and the Environmental Protection Agency.

Finally, it would be possible to assign oversight of genetic engineering to the body that succeeds the present Commission, if any. This arrangement would permit the ongoing oversight of this field to be integrated into the consideration given to the implications of other important developments in the biomedical arena. Of course, that would also mean that the focus would be on the explicitly medical aspects—with limited expertise for other areas such as agriculture and patenting. The assignment would, however, recognize that the flow of work in this area is not always at a constant pace; a group with a more diverse mandate, such as the President's Commission, could turn its attention to other areas rather than wasting time when there is no immediate issue of gene splicing to be considered, while still being ready should such issues need prompt attention.

Whatever mechanism is adopted, its major impact will rest on its ability to educate and to persuade. It must set its sights high if it is to function as an agency for the protection for the future. Protecting the future sometimes means acting with vision and spirit as well as with humility—and striking a balance between courage and prudence will not be an easy task.

Thank you.

[The prepared statement of Mr. Capron follows:]

STATEMENT OF ALEXANDER M. CAPRON
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of the

President's Commission for the Study of
Ethical Problem in Medicine and
Biomedical and Behavioral Research

on

Ethical and Social Issues
in the Application of Genetic Engineering
to Human Beings

Before the

SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT

COMMITTEE ON SCIENCE AND TECHNOLOGY

UNITED STATES HOUSE OF REPRESENTATIVES

November 16, 1982

Good morning Mr. Chairman and members of the Committee. Morris B. Abram, the Chairman of the President's Commission, regrets that he is unable to be here this morning and has asked that I provide you with an overview of the ethical and social issues raised by the human uses of genetic engineering. This has been one of the topics that the Commission has examined over the past several years, and last Friday, agreement was reached on a draft report.

The Commission's study--like your Committee's hearings over the next several days--focused on one particular and very important aspect of scientists' newly gained ability to manipulate the material that is responsible for the different forms of life on earth. The Commission has been centrally concerned with the social and ethical implications of applying "gene splicing"--as this technique is known--directly to human beings.

The Commission began it study in September 1980, in response to the request of the President's Science Advisor. Urgent concern had been expressed to the President earlier that year by the Nation's three major religious associations that no governmental body was "exercising adequate oversight or control, nor addressing the fundamental ethical questions."

In some ways, the Commission has found this concern to be well-founded. The Recombinant DNA Advisory Committee (known as RAC) at the National Institutes of Health has issued guidelines for government-sponsored laboratory research with gene splicing, and researchers in privately sponsored labs and industrial concerns have affirmed their adherence to these standards; agencies with regulatory responsibilities are either dealing with gene splicing (such as the FDA's recent approval of human insulin produced in this fashion) or are at least preparing to do so (as seems to be the case with the EPA and OSHA). Yet none of these agencies has focused particularly on the direct human use of gene splicing nor upon the ethical questions.

These questions have been addressed--although certainly not resolved--by the Commission. In sharing some of our thinking with you today, I want to emphasize that the Commission sees its major contribution as sorting out some of the issues and stimulating thoughtful discussion of them over the long term. We have no intention of truncating such discussion with what would of necessity be premature conclusions for a field that is unfolding rapidly and in ways that cannot be precisely foretold. I think it would be accurate, however, to say that while we have found that the religious leaders were correct in perceiving a lack of governmental oversight, we have not found in the gene splicing now being planned or undertaken the "fundamental danger" to human values, social norms or ethical principles that alarmed them.

THE ORIGINS OF CONCERN

The public's attention was first drawn to implications of genetic engineering by the actions of scientists concerned about the safety of their laboratory research with micro-organisms. Although the political public and scientific debate was focused on laboratory hazards, it become apparent that the implications of gene splicing were more far-reaching. Indeed, in some ways, the success of laboratory experiments--which lead toward the use of gene splicing in industrial settings, in the general environment, and in medical treatment--only heighten those anxieties.

In reviewing statements about gene splicing in the popular press, I have been struck by the frequent invocation of what Willard Gaylin some years ago called the "Frankenstein factor." The analogy is illuminating for several reasons. First, Dr. Frankenstein was a creator of new life and the gene splicers have raised questions about mankind's role as creator. Second, Dr. Frankenstein's creation was a frightening monster and gene splicing has raised fears about strange new life forms. These have often been expressed in terms of "interfering with evolution." Some scientists have been concerned about the hazards created when the "barriers" against transfer of genetic material between species are breached. One of the results of research in this field, however, has been new understanding of the ways in which genetic material moves about within and between cells, meaning that some of the evolutionary barriers are less rigid than they were once thought to be.

The Frankenstein story also reminds us of the tale of the Sorcerer's Apprentice--in both, a development intended to be beneficial proved to be dangerous when it got out of control. Likewise in gene splicing: as Erwin Chargaff, a biochemicist who has been particularly critical of the field, remarked "you can stop splitting the atom, you can stop visiting the moon, you can stop using aerosols...but you cannot recall a new form of life."

The Frankenstein analogy also comes to mind because of people's concern that something is being done to them and their world by individuals concerned with their own goals but not necessarily with human betterment. As C. S. Lewis once observed, "Man's power over nature is really the power of some men over others with nature as their instrument." Stated more pointedly by Alfred E. Vellucci, the Mayor of Cambridge, Massachusetts, during his city's debate in 1976 about a Harvard genetic engineering lab, "I don't think these scientists are thinking about mankind at all. I think they're getting their thrills and excitement and passion to dig in and keep digging, to see what the hell they can do."

But most particularly, it seems to me that the Frankenstein story was on the lips of many people--both scientists and lay people--because it dealt with the creation of a new being with a human form. Ultimately, the concerns about laboratory risks are not enough to explain the public or the scientific fascination with this topic. There are certainly other forms of research that pose comparable danger that have never excited as much public discussion. In the end, it is the potential human uses of the technique that are on people's minds.

THE BASIS OF GENE SPLICING

Before discussing the issues raised by the field, it might be helpful for me to say a few words about techniques and their uses. I'm sure that subsequent witnesses will provide you with greater detail on these and related subjects.

First off, I should mention that we did not examine *in vitro* fertilization (so-called test-tube babies) or cloning of organisms, which are reproductive rather than genetic technologies that might be useful in certain applications of gene splicing but do not necessarily involve it.

I believe your committee, through a number of past hearings, is well-versed in the history of gene splicing--from Crick and Watson's proposal in 1953 of the double helix as the structure for DNA to the artificial creation of genes in the laboratory and the actual manipulation of DNA in the last decade.

The Commission examined three ways in which gene splicing may enter into the treatment of human beings. Moving from the most near-at-hand and familiar to the most far-off and controversial, they are: the production of useful drugs and biologics, the diagnosis of genetic diseases, and the cure of such diseases.

Genetically Engineered Drugs and Biologics. I think you have already heard a good deal about the first of the subjects, particularly the use of recombinant DNA techniques to create bacteria capable of producing desirable medical products--like interferon or human growth hormone. The good and bad consequences envisioned in many aspects of gene splicing are often exaggerated, and this aspect is no exception. The very ability of bacteria to multiply rapidly--a single cultured cell can produce more than a billion copies of itself in less than 15 hours--would seem to endow the gene splicers with a biological Midas' touch. While many of the hormones, enzymes and other produces being sought are in short supply from natural sources, even production through recombinant bacteria will not be cheap, as shown by the recently licensed human insulin.

Nonetheless, even reining in the tendency toward inflated claims, it does seem likely that drugs and vaccines produced through genetic engineering will play an increasingly important part in medical treatment and even to the point of opening up avenues of treatment that were not previously available. A particularly important area is the development of monoclonal antibodies through a technique called cell fusion. This method--which involves literally fusing together the genetic material from the cells of two unrelated species--is one of several that offers the hope to cancer researchers that they may someday soon have methods of diagnosis and treatment which will cause us to look back on today's methods as we now regard the use of leeches and purgings.

The concerns raised by this aspect of medically oriented gene splicing are basically those that have attended the field for the past decade--namely the laboratory (and now the industrial) biohazards to workers and to the larger environment--and those that accompany the initial human use of any new product. These matters are by now familiar to policymakers and, while deserving of careful attention based upon the particular facts of each individual development, are not ones that the President's Commission found to be at the heart of the present subject. Ethical issues are certainly involved--including not only the respect due to persons involved in research but also issues of fairness in the distribution of what may be a life-saving product once developed and proven safe and effective. However, they are no different from the issues raised by drugs and biologics produced by other, non-gene splicing methods.

Diagnosis of Genetic Conditions. The second area in which gene splicing can be applied in medical care--namely in genetic screening and diagnosis--has also recently begun bearing fruit. Through the use of restriction enzymes--of which 150 have been discovered--it is possible to cut the strands of DNA at particular, known points. This technique holds great promise for genetic disorders or carrier status that until now have not been readily diagnosable because present testing methods look for gene products rather than for the genes themselves.

The details of the techniques need not detain us now. Suffice it to say that in some cases--as has already been shown with hemoglobin disorders--a restriction enzyme site occurs right at the relevant gene, while in the variant ("defective") gene the restriction site is absent, so that when the DNA is cut, a segment of a different length is produced, which indicates the defective gene. In other cases, the cutting-point is in a stretch of DNA adjacent to the gene of interest; then it is necessary to do familial studies to find this linkage.

Potentially, the technique would not be useful in prenatal and carrier screening for recognized "genetic defects" but in detecting the presence or absence of genes associated with other conditions or characteristics.

Care of Genetic Disorders. The most and novel important area, from the Commission's viewpoint, is in using gene splicing to cure genetic disorders. If this proves possible, it would differ from other treatments because it would not involve the manipulation of the patient or the application (often continually) of a drug but the actual alteration of the cause of the condition itself. Such steps have not yet been successfully undertaken but they are coming closer every day. Several recent developments are particularly important regarding human applications.

First, because scientists do not yet fully understand how genes are regulated, it has been difficult to induce expression of foreign genes inserted into cells--that is, to get the gene to function and program the cell to produce the relevant protein. Remarkable progress has been made lately, however, and scientists have been successful in getting recombinant genes to function in multicell animals and even in correcting a gene defect--a feat accomplished in fruit flies through the discovery of what are termed "transposable elements." Although the counterparts of these elements have not yet been found in man, this experiment points the way to the future therapeutic uses of gene splicing. Second, there is the question: can the changes brought on by gene splicing be passed on to subsequent generations? In experiments with mice, this important effect has now been demonstrated.

The Commission divided gene splicing in humans into two categories: somatic cell treatment and germ cell treatment. In the first category, some people have distinguished between "gene therapy," in which a "normal gene" is introduced anywhere it will function in the patient's DNA, and "gene surgery," in which the "defective" gene is also excised or at least its function is suppressed, so that the inserted gene does not have to compete with the old one. This difference is of greater concern medically than ethically.

Basically, somatic cell treatment would probably initially be directed at single gene mutations, which are now known to cause more than 2000 human disorders. If the disorder involves an identifiable cell product of a discrete subpopulation of cells, treatment might involve the removal of some or all of these cells, genetic alteration, and their reinsertion into the patient. Thus, the technique is basically organ transplantation--except that the physicians are altering the patient's own organ rather than using another human being's organ. From the viewpoint of medical ethics this may be no small matter, because of the greater uncertainties, but conceptually it is no different--provided that we have agreement on what constitutes a "disease" for which "therapy" is appropriate.

When the attempt to change a person's genes involves a systemic application of the new gene, a chance (although one that may prove to be very small) arises of altering germ-line cells as well. Furthermore, certain diseases--like cystic fibrosis--would have to be treated early in development; if the gene splicing took place at the embryonic phase it would probably affect all cells in the body. Although treatments of this sort are almost certainly further in the future than other therapeutic uses of gene splicing, they raise much more troubling issues. First, there are the special ethical problems of creating human beings with the intention of altering them--entirely without their consent. Second, there are the social and biological concerns over deleterious changes that rather than being limited to one person or one generation would become part of the human genetic inheritance.

ISSUES OF MEANS

In light of people's understandable anxieties about genetic engineering as applied to human beings, what are the central issues that the Commission preceived arising in this work?

The first is the question of forbidden knowledge. In the view of Robert Sinsheimer, a leading biologist at Caltech, "We must face the fact that there can be unwanted knowledge." It is true that the potential understanding of the machinery of life is an awesome prospect. Like the new knowledge associated with Copernicus, Darwin, Freud and Einstein, that associated with the gene splicers offers further challenge to human beings' conception of themselves as the unique and even sacrosanct center of the universe. By identifying DNA and learning how the manipulate it, science seems to have reduced people to a set of malleable molecules that can be interchanged with those of species that people regard as inferior. Yet, as disorienting and perhaps even disruptive as the new knowledge may be, the Commission rejects the idea that it should be regarded as "forbidden."

Yet, unlike the earlier revoluntary discoveries those in molecular biology are not merely descriptive; they give scientists vast new power for action. The use of these new powers has frequently been labelled "playing God." This description carries with it an implication that it is wrong for human beings to engage in this activity at all--that we have overreached ourselves by pretending to have God-like powers.

This objection--that in creating new life forms scientists are abusing their knowledge by interfering with nature--has several possible meanings. At least one is not persuasive. For millenia, people have intefered with nature both intentionally, through the breeding of new varieties of plants and animals, and unintentionally as a side effect of other human activities, including medicine itself. There is some difference in aspects of gene splicing, however, that might create hybrids that are capable of reproducing themselves--but here the concern would not be that crossing species lines is inherently wrong, merely that if the effects are deleterious their harm may be multiplied by their perpetuation into later generations--like a recombinant DNA Dutch elm disease. This is an issue that deserves to be treated with great care, but it is not one that raises a problem of principle.

There is, however, another aspect to the complaint about "playing God" in crossing species lines where a prohibition may be in order, and that is in the hybridization of human beings with other living things. Present research is entirely at the cellular level--such as the fusion of human cells with those of mice--or through the insertion of a single human gene, such as the gene for insulin production, into a micro-organism.

The prospect of creating an actual being with partically human characteristics offends a deeply held taboo. There is, however, no legal or regulatory prohibition of such a step. And if the barrier is to survive in the face of scientific advances, the reasoning behind it will need further attention. It may, for example, be fruitful to clarify what it is about human beings that is unique--whether it is the sum of their characteristics or the possession of particular characteristics? There is a certain irony here since a person approaching the subject from a religious or philosophical position is likely to deny that human beings are simply a reflection of the particular chemicals that make them up, and yet the objection is being raised is to an alternation in those chemicals.

ISSUES OF CONSEQUENCES

When one moves from absolute prohibitions on the human uses of gene splicing to questions of particular consequences, one is faced immediately with a realization of the great uncertainty in this field. The uncertainty is more than a question of whether a particular event will occur but also encompasses the ethical uncertainty that follows from not knowing whether a use of technology should be regarded as beneficial or harmful and even the conceptual uncertainty that comes from new developments that challenge people's fundamental beliefs. Let me highlight some of these issues very quickly for you.

There is first the concern for personal health. This concern has several bases--for example, the notion that in replacing a particular DNA sequence that is regarded as deleterious a physician might also unintentionally be removing other genetic material that is in fact beneficial. This concern rests in part on the fact that scientists do not know the purpose of a great deal of DNA in the human chromosones. Much of it is thought not to "code" at all, which is in some ways a puzzling finding. Moreover, even when only a particular gene is replaced there is a risk that some advantage supplied by the gene may be lost. Although the existence of such an advantage is a matter of debate--sickle cell is the only condition on which there is general agreement--it is not a concern that can be easily dismissed in our present state of ignorance. Furthermore, little is known about the range of effects a single gene can have, though. many effect several parts of the body in what appeared to be a wide variety of ways. All of these concerns illustrate issues of personal well-being that will arise with the human uses of genetic engineering. To deal with them, IRBs at research institutions will need to be able to draw on the expertise of people knowledgeable about human genetics and particularly about gene splicing.

Second are questions of inheritance. The possibility that genetic changes would be inherited raises many questions. For example, would such alternations be so widespread in society that the "gene pool" would lose desirable diversity, thereby exposing mankind--like some inbred strain of rice or corn--to the risk of decimation by a newly arising pathogen. Although this concern is not yet pressing, decisions made now about gene splicing may affect society's ability to respond to this issue when it becomes a scientific possibility.

Beyond any physical consequences for further generations, the ability to change one's genes challenges the basic assumptions about people's links to, and responsibility for, their progeny. In some ways, one's responsibility may be increased--will it be acceptable for people simply to accept the results of the natural lottery by which characteristics are now determined or will "responsible parents" be expected to "correct" bad genes and to augment others to give their children an opportunity for a higher level of physical or cognitive functioning? On the other hand, knowing that future generations may employ an even more advanced technology to alter or to replace characteristics passed onto them may weaken people's sense of genetic continuity. Furthermore, by blurring the line between what counts as a serious defect or disability and what is "normal functioning," gene splicing may alter our perception of what society owes to children, particularly those burdened by handicaps.

The potential of gene therapy or surgery to improve functioning calls into question the scope and limits of a central element of a democratic political theory: the commitment of equality of opportunity. Would genetic engineering become mandatory--along, perhaps, with restrictions on "natural reproduction"--in order to avoid the effects of the "natural lottery" that has such a profound influence on our opportunities in life?

Any discussion of equality leads naturally into a discussion of justice. Who should decide which lines of genetic engineering ought to be pursued and which applications of the technology to which patients ought to be undertaken? This is a question that seldom arises about medical progress. Decisionmaking in medicine is widely dispersed, resting upon the tripod of peer standards, patient consent and very broad and general state regulation--although this third leg of the tripod is receiving greater attention because of the extensive involvement of the state with the financing of medical care. But if genetic engineering comes to be seen as a very benefical and powerful form of treatment, questions will certainly be raised about access to it not only in the use of techniques that have been developed but also deciding about which areas need to be pursued. It seem to me that this issue lies behind the concerns that have been expressed by many about the effect of commercial involvement in the basic research carried on by academic and other independent institutions and about the effects of such control on the availability of dispassionate expert advice for policymakers.

ISSUES OF CONCEPTS

Several of the other issues addressed by the President's Commission remain very diffuse although they are regarded as matters of importance. First, there are the questions raised about the effects of gene splicing on our sense of personal identity. The current tendency is to think of a person as an individual of a certain character and personality that, following the normal stages of physical, social and physocological development, is relatively fixed within certain boundaries. But this concept--and the sense of predictability and stability in interpersonal relations that it confers--could quickly become outmoded if people are able to use gene splicing to make basic changes in themselves over the course of a life-time. Of course, existing forms of medical treatment--particularly in the psychological and psychosurgical fields--can make profound changes in people. The sense there, however, is that of restoring a person to the self from which a disorder has caused him or her to deviate, not of creating a "new person," as is potentially the case with gene splicing. Of course, the prospect for gene splicing of this sort is very remote, since the aspects of a person in question appear to be caused by a complex interaction of numerous genetic and environmental factors. The issue, however, is important enough to receive further attention.

Similarly, a question arises about the alteration of the genetic basis for the natural characteristics of all human beings--that is, a change in "human nature." Basically gene splicing of this sort would raise many of the same concerns I mentioned earlier regarding the hybridizing of a human being with another species. Yet this development seems less like science fiction, since changes may be introduced more gradually as the ability is gained to change particular characteristics one-by-one. At what point, and regarding which human qualities, would one say that a change in human nature has been made and how would one know whether such a change is desirable? Obviously this is not yet a pressing issue--particularly when compared with the use of other techniques of indoctrination and behavior control that are already available to make some people act in ways that many would think "go against human nature." Yet, it is worthwhile remembering in this and other contexts that developments in the field of gene splicing have come along more quickly than many had predicted. Therefore, one cannot assume that the day will never come when scientists will be capable of deliberate, selective and rapid alterations in the genetic basis of what is distinctly human.

ATTITUDE TOWARD THE ISSUES

Although the Commission has found that the issues raised by gene splicing in human beings can better be taken into account by biomedical scientists, government officials, and the public if they are considered individually, it would be a mistake to respond to the new technology solely by reducing all concerns to assessments of particular consequences or applications. Even after the potential consequences have been carefully sifted and their implications for human welfare have been explored, there remains an important residual concern expressed by the warning against "playing God." It not only reminds human beings that they are only human and will some day have to pay if they underestimate their own ignorance and fallibility, but it also points to the weighty and unusual nature of this activity, which stirs elusive fears that are not easily calmed.

At this point in the development of genetic engineering no reasons have been found for abandoning the entire enterprise--indeed, it would probably be naive to assume that it could be. To expect humanity to turn its back on what may be one of the greatest technological revolutions may itself betray a failure to recognize the limits of individual and social self-restraint.

Assuming that research will continue somewhere, it seems more prudent to encourage its development and control under the sophisticated and responsive regulatory arrangements of this country, subject to the scrutiny of a free press and within the general framework of democratic institutions. Efficient regulation and oversight will require considerable division of responsibility among different bodies and agencies. Legal controls will necessarily focus on the prevention of tangible harms to individuals and the environment. Nonetheless, the Commission believes it is crucial that those entrusted with such oversight and regulation do not lose sight of the more elusive, but equally important, concerns about the human significance of genetic engineering or neglect such concerns because they do not fit neatly into existing institutional jurisdictions.

MECHANISMS FOR OVERSIGHT

In light of the important issues to which the Commission has given preliminary examination, it seems reasonable to seek to find one or a number of means of continuing oversight in this field. Unlike the situation eight years ago, however, when the risks seen in the initial research with gene splicing lead to the imposition of a voluntary moratorium of certain lines of research, the creation of the RAC, and the issuance of government regulations, there is no need for a sense of panic. It is the profound and fundamental nature of the issues at stake and not their immediacy that counsels the creation of appropriate means of oversight.

In looking to the future, the Commission reached several conclusions about the design of any oversight group. Briefly, they are, first, that the group should regard education as a prime objective. Second, that it should have a role of leadership as well as oversight within the Federal government--meaning that it should, at a minimum, have "action-forcing power." Third, it should have a diverse membership and ought to conduct its work in public. Fourth, it should have means of drawing on disinterested expertise on a wide variety of scientific and technical issues. Fifth, it should treat in an unified framework all the issues raised by genetic engineering--including industrial as well as laboratory safety, environment hazards, agricultural and commercial opportunities and pitfalls, international ramifications, biomedical effects on risks, and social and ethical implications. Sixth, in so far as possible its oversight functions should be separated from any sponsoring functions so that no conflict-of-interest will arise of the sort that plagued the old AEC.

As a practical matter, the Commission saw great value in building on the history, largely regarded as successful, of RAC. Indeed, it seemed to the Commission that Dr. Donald Fredrickson, whose term as Director of NIH was coincident with that of RAC's major development, was correct in suggesting that the time has come for a "third generation" RAC. Rather than recommending a particular method of oversight, the Commission proposes a number of possible formats, as starting points for consideration by the President and Congress.

One means of supplementing a less active RAC--now that many of the laboratory biohazards are no longer regarded as pressing matters--would be through a mixed public-private sector body such as those that have operated in other areas. Alternatively if it is felt that the extent of Federal responsibility is so great, both for safety and for promotion of this field, that a governmental body of greater breadth than the present RAC is needed, the interagency committee established in 1976 (which has been inactive for the past several years) could be reinvigorated. This would have the advantage of direct involvement of the leading Federal agencies but the disadvantage that its membership is entirely governmental and its meetings are not subject to the Federal Advisory Committees Act.

Another format would be the creation of a Genetic Engineering Commission (GEC) of 11 to 15 members from outside the government, which could meet regularly to deal solely with this field. This group could have a majority of non-scientists, with the ability to draw on a series of technical panels to provide expertise not only in laboratory, agriculture, manufacturing, and medical areas but also matters involving international controls. In order to coordinate with the Federal agencies, it could draw on a panel of liaison officers from the Departments of Agriculture, Commerce, Defense, Energy, Health and Human Services, Interior, Labor and State as well as the National Science Foundation, the National Endowment for for the Humanities, and the Environmental Protection Agency.

Finally, it would be possible to assign oversight of genetic engineering to the body that succeeds the present Commission, if any. This arrangement would permit the on-going oversight of this field to be integrated into the consideration given to the implications of other important developments in the biomedical arena. Of course, that would also mean that the focus would be on the explicitly medical aspects--with limited expertise for other areas such as agriculture and patenting. The assignment would, however, recognize that the flow of work in this area is not always at a constant pace; a group with a more diverse mandate, such as the President's Commission, could turn its attention to other areas rather than wasting time when there is no immediate issue of gene splicing to be considered, while still being ready should such issues need prompt attention.

Whatever mechanism is adopted, its major impact will rest on its ability to educate and to persuade. It must set its sights high if it is to function as an agency for the protection for the future. Protecting the future sometimes means acting with vision and spirit as well as with humility--and striking a balance between courage and prudence will not be an easy task.

Mr. GORE. Thank you very much for excellent and thought-provoking testimony to say the least.

Let me explore some questions with you.

You are recommending, through the Commission, the Commission is recommending a new Government oversight body. But you are not saying exactly where that responsibility should lie. You are instead listing the characteristics you would like to see such a governmental body have. Is that right?

Mr. CAPRON. That is correct.

Mr. GORE. Would you like to see it independent of the NIH or not?

Mr. CAPRON. Our sense is that the present RAC has done a good job. Yet, as the area continues to develop, the kind of tensions that for a long time persisted with the Atomic Energy Commission, which was both a sponsor and a regulator of its field, are going to come increasingly to the fore, and therefore it would be advisable to have an oversight body have the independence of the NIH or any of the other groups that are sponsoring research. The NIH is not the only sponsor of research, although it has been the major governmental sponsor of research.

Mr. GORE. This will likely require action by the Congress to establish such a governmental body. You said it should deal with more than simply the bioethical questions. What did you have in mind?

Mr. CAPRON. Well, many of these developments are synergistic. They go hand in hand, they feed each other. And so, the applications for human use of a development in an agricultural area may be quickly perceived. It therefore would seem advisable for the group to have a broad base, because genetic engineering is going to have ramifications in the workplace, in the general environment through agricultural, industrial, mining uses, petrochemical uses, and so forth. And a single body that could bring together the focus, I think would be one of the things the Commission found to be advisable.

That breadth shouldn't obscure what are going to be some of the major issues. We haven't looked at those issues as they arise, for instance, in agriculture, but there are some concerns expressed about the effect of genetic engineering techniques in worsening certain aspects of the diminishing gene pool that exists in certain agricultural areas, where heavy reliance on a single strain of corn or rice or the like does create risks, and whether or not the most modern techniques are being used to preserve the wide variety of present germ lines that exist in the agricultural field.

All those are issues which have important ramifications for human beings, and will continue to need oversight.

Mr. GORE. It is likely this subcommittee will recommend to the full Science and Technology Committee legislation to establish a new Government oversight body to deal with these broad questions.

Now, second, if I am not mistaken, in your presentation you said that a recent survey found that two-thirds of the American public would halt the development of this technology.

Mr. CAPRON. Well, yes, that is what the National Science Foundation study said, that genetic engineering should not be pursued. And I mentioned it before going into these particular techniques to emphasize that I think the public is not yet well educated about what that means, and does have many misconceptions about, as I said, the scientists dipping into some genetic soup and creating a mixture in one way or another that could be frightening.

Mr. GORE. Well, you know, I think there is a problem with possible overreaction on both sides.

I understand what you are saying. You are saying that the fact that two-thirds of the American people would like to see this technology stopped dead in its tracks is probably based on some of the scare stories that have gotten out about it. But I think science would be ill-advised to dismiss the concerns of the American people, because they may have some—they may be grasping some truths that the specialists are not.

If the scientist is going to proceed, then there must be a full-blown sensitive and subtle discussion of the bioethical questions involved. And scientists, whether industry or universities, must be prepared to flag for the public issues and implications that arise out of their research at the earliest possible stage. Otherwise, there will be a growing public reaction against the development of the technology. And that would be unfortunate.

In fact, one could say that where a particular line of inquiry has the promise for curing a disease like cancer, it would be unethical not to develop that cure. Would you agree with that?

Mr. CAPRON. Well, the ethics of pursuing or not pursuing certain lines of research is a very complex question. There is certainly a limited number of resources which we as a society have. And at any one time, people are not necessarily pursuing every possible means of improving the human condition.

So I would not say flatly that any time one saw that there was a possible line of inquiry that could lead to a cure, that not pursuing it is not ethical. One has to ask what else can one do with one's resources at that time. Certainly, it could come to the point that withholding a treatment from a particular person may be unethical.

If I can comment on the observation you made a moment ago, Mr. Chairman, I think your comments are likely to spread some fear and trembling to the scientific community when they hear you saying that the public's concern that this line of research ought not to be pursued should be heeded.

I would say that the best reassurance against inappropriate reactions from public institutions is the establishment of bodies that have understanding of the field and do reflect the public views. In fact, that is one of the reasons the Commission recommends that any body not have a majority of scientists on it, that it has to be broadly based in society, and not be just a reflection of the scientific or expert group.

The existence of the Recombinant DNA Advisory Committee thing went a long way to reassure the public about the specific risks it was dealing with, the biohazards, and even at a time when certain revelations were made, for example, about Dr. Cline's experiment at UCLA, the fact that the Government had means of dealing with that, was prepared, had reviewed those issues it seems to me was a great reassurance to the public that there was no reason for panic here.

The Government was not being caught unawares by the development.

Therefore, I would hope that medical scientists and other scientists concerned with this field would welcome the opportunity to create an institution that would be properly sensitive both to the desire to advance science and to the need to take into account the awsome powers that are created and their proper uses.

Mr. GORE. Well, I don't disagree with what you are saying and when I said earlier, scientists in the field should take note of the great public concern by heeding it, what I meant and what I said was that they should be extra careful to flag for the public issues as quickly as they arise that have bioethical implications.

I believe that it would be reassuring to have a Government body of the kind that has been discussed and this subcomittee will almost certainly recommend the establishment of such a Government body but I don't think that is enough.

I think there must be a wide public discussion of these questions, otherwise, I think that the reaction to which I alluded might well occur in spite of whatever Government body was established.

I think you are quite correct in pointing to the handling of the concerns about uncontrolled spreading of mutations in the laboratory, earlier that whole safety issue with the DNA research.

I think you are correct in pointing to that as a success story. It as handled as well. There were concerns raised.

Some of the people raising the concerns were scientists themselves.

A focused sustained effort was made to find out exactly what the basis of these concerns was and then there was a lot of reassurance when they were fully understood. But in this case we are dealing with something different. We are not dealing here with the possible consequences of mistakes. We are dealing with the consequences of success.

Mr. CAPRON. Agreed.

Mr. GORE. As science is defining success and the incessant pushing forward the frontiers of knowledge, to use the old cliche, is creating new potentials that are just very troubling to people.

Mr. CAPRON. One of the complications this adds—which complicates the desire that you have expressed and which I would applaud to see scientists themselves initiate the discussion and draw to people's attention those aspects of their work that raise questions—is that it is much harder for a responsible scientist in this area to know what parts of his or her work raise those questions because the questions themselves are not simply the questions of direct physical harm.

That was the question of the biosafety issue—was a person going to come down sick because of some mutant organism? Here we are talking about the kinds of issues that I have reviewed here which I am sure, even after the Commission has reported on them seem very amorphous, they are very hard to put your hands on. What is meant when one says you are playing God, what does that mean? What does it mean to change nature? Is that possible? What characteristics? When should I be concerned if I am a scientist and I think you do have to have some ability to deal with those issues but they are not going to be dealt with as easily?

Mr. **Gore**. Well, I think the kind of sustained public discussion of these issues that I believe is necessary would be useful not just to inform the public but to inform the scientists as well as to what the implications of their research might be. I think that is greatly needed.

Let me, by way of example, point to a subject in your report that I know you and others were concerned would be blown out of proportion and I want to treat it with a sense of proportion. But you mentioned in your presentation here this morning as well. You said that there might well be a need for a prohibition on hybridization of human beings.

Now, at what point would you have such a prohibition, before the first human genes are put into mice? That has already occurred.

Mr. **Capron**. One is talking there about a single gene, and I think one of the reasons I came back to the subject was to say that it is more likely that this sort of thing would occur incrementally through the additions of this characteristic and that, rather than through the merging together of a chimpanzee and a human being or something.

Mr. **Gore**. Which is theoretically possible. The insertion of human characteristics?

Mr. **Capron**. I guess you can say yes, theoretically. A dozen years ago, Charles Remington, who is a professor of biology at Yale, wrote up for a book that I was working on, "Human Experimentation," a protocol for the breeding of a chimpanzee and a human through the artificial insemination of a chimpanzee. The purpose of that was to then go on and discuss why ethically that experiment could not be done. But his explanation of why it would be interesting to do had all to do with tracing human development. This is in the days before genetic engineering, some of the very things that genetic engineers are now interested in doing, seeing what the effect of certain genes are on development, and many of these experiments are being done not because it is desirable to change the color of fruit flies' eyes but because it is desirable to learn how individual genes affect human beings.

Mr. **Gore**. But there is a danger in even discussing an example like that of sensationalizing the potential of the technology in a way that inhibits a meaningful discussion of it. But I think that it is important to look at the continuum of possibilities and it is relevant to the point that I was making earlier. There are possibilities coming out of this technology that are and will be abhorrent to people in this country and I would hope elsewhere in the world.

And since it is very difficult to draw the line and say on this side of the line it is OK and on the other side of the line it is abhorrent, for that reason it is extremely important for there to be the full public discussion and for scientists to be fully aware of the strongly held concerns on the part of the public.

Mr. **Capron**. I agree with you, but the difficulty is that when one comes at it through a direct hybridizing you are talking about something that is immediately, let's say, a 50-percent human and 50-percent some other species and that is what is abhorrent.

When you are coming at it from the other end of the spectrum by the addition of nonhuman characteristics to a human being or the addition of many human genes and, therefore, one expects, human characteristics to a nonhuman species, one comes toward that incrementally. As you say, it is thus very difficult to know at what point one would say, "That should not be done because you are beginning to approach this forbidden land of the half human, half something else."

I don't think that I have any answer for how that line is drawn today. Fortunately, we are not near it, but we ought not to forget that that prospect is there.

Mr. GORE. Well, the public is going to insist and demand, I believe, that we find out how to draw that line and that we come up with the meaningful criteria to assist us in that judgment.

I think that it is going to have to be done.

You say that we are not near that. We are not near the far end of the spectrum, no. But in between the first draft of the President's Commission's report and the second one, this year, the experiments to put human genes in mice took place and I think caused a reevaluation by the Commission of how rapidly this field was advancing; is that correct?

Mr. CAPRON. Well, I think the experiments with the fruitflies that were reported in October were particularly significant. That was not a human gene in that case. That was the real step in showing that one can achieve a correction in a genetic defect.

Mr. GORE. That is passed on to succeeding generations.

Mr. CAPRON. That is passed on to succeeding generations, yes.

Mr. GORE. Now, the Commission began its inquiry as a result of a formal request to the former President Carter by the National Council of Churches, the U.S. Catholic Conference, and the Synagogue Council in 1980; is that correct?

Mr. CAPRON. That is right.

Mr. GORE. And that was 2 years and 2 months ago.

Now, in that early draft that you came out with in July, you said the Commission "has found no ethical precepts that would preclude the initial clinical uses of gene splicing now being undertaken or planned or the research procedures through which knowledge is sought."

Has that been taken out of the final draft?

Mr. CAPRON. No. That conclusion remains the same. I can't say the wording is exactly the same because it has been through a lot of changes but the conclusion remains that there is no barrier for the kinds of uses that are being talked about for therapy on a particular individual. Indeed, as another example, the type of treatment of beta thalassemia which was attempted by Dr. Cline 2 years ago using recombinant DNA modified cells from the individual has now been apparently successfully accomplished using donor cells from a sibling of the individual. The difference is that in one case, cells that are completely foreign to the individual; namely, from the donor, are used to overcome the thalassemia, and in the other case, the person's own reengineered cells are being used. But certainly progress on the one indicates that what we are talking about is not a radically different form of treatment than treatments that are apparently coming to be acceptable, such as the donor thalassemia case.

Mr. GORE. Now, what you are saying is that if other normal, ethical analyses are done which evaluate risk and safety and benefits and what is best for the patients, if the traditional analysis of a proposed treatment indicates that the doctor should go forward, you are saying that there should be no special bar to genetic therapy if those other criteria are satisfied?

Mr. CAPRON. Right. Those criteria are more complex in a genetic area because it is so new but there is nothing inherently wrong.

Mr. GORE. Yes. We are, however, at that point, crossing a threshold?

Mr. CAPRON. I think so, and that threshold has some other implications for people's concepts and for those questions of uncertainty that I tried to identify, the sense that one's genes are fixed in a personal sense. That is, a personal sense that we all have about ourselves that we are going to be the same person throughout our body—all the cells have the same genetic information—and it has been that way since we were conceived. That is now up for grabs. That wouldn't be true of a patient who had been treated this way.

Mr. GORE. Now, because we have to treat people who are ill, because we have an ethical obligation to do so and because we have the desire, we want to do that and these techniques become available, then we do the traditional analysis and we say, yes, let's go forward.

But at that point we cross a threshold on the other side of which are all of the possibilities and potentials that are troubling to people as well as many that are exciting that have not been as widely discussed.

So we have an obligation as a society, at the time we cross that threshold to fully inventory as fully as possible what the likely implications are and make those choices that are best for us being aware of the fact that precedents are being established and will be established in these early stages that will lead us along one of many paths and make it more difficult to go back and make different ethical and bioethical decisions later on.

Mr. CAPRON. I would agree with that and if I might come back to a point you made before, you said isn't it ethically obligatory to do this and then in discussing the genetic engineering you say we might be ethically obliged to do this or that.

In part, the sense that if you can do something that might have a benefit to a person one is ethically obliged to do that thing is one of the forces that creates what is potentially a slippery slope. And if we look at certain things and say these immediate ones are acceptable but those further down are not, we have to see some reason that there is a barrier between them, where we come to a logical stopping point. One of the things that breaks down a logical stopping point is the sense that it is ethically obligatory to do anything that has any potential benefit.

When I mentioned in testimony that the decisions we make now about how this would be controlled and how decisions will be made will have real impact on the later things, that is exactly what I had in mind. It becomes particularly important when one thinks about parental obligations to children. "Because of our obligations to children, people are already saying, as to certain forms of prenatal treatment," doesn't this raise a concern that we might be obliged as good parents to do this for a child even if we would have questions or scruples about it or even if other alternatives would seem preferable?

Those are the kinds of things which make a slope potentially slippery if we say there is no way of stopping once we get onto it.

Mr. GORE. What about the possibility of correction of imperfections that most would regard as whimsical? For example, the change of traits for reasons that are not related to the survival of the individual but are related to the preferences of the parents?

Mr. CAPRON. I think we should begin re-recognizing that those types of traits are believed to be largely multifactoral and so we are talking about something that is not too immediate.

I know we have the press here with us and we don't want to give the image that what is being talked about is something that could be done right away as soon as any form of genetic surgery or genetic surgery is available. But, yes, I think that is a legitimate concern.

Mr. GORE. Well, later witnesses are going to say that that will be possible before very long and that the traits which can be selected involved not just physical characteristics but mental charcteristics as well.

Mr. CAPRON. Well, the general question of "enhancement," as we refer to it in our report, or augmenting a characteristic rather than remedying what is widely agreed upon as a defect is problematic for two reasons. The first is the identification of exactly which kinds of characteristics would, indeed, be acceptable to remedy. It is like the biohazards issue again. Everybody can agree that hazards are bad and everybody can agree that certain diseases are bad and, therefore, treating that doesn't raise questions the way avoiding hazards doesn't raise questions. The other side of the line is much more amorphous.

The second problem that comes up here is the question of inheritance again. If we are making these kinds of changes in human beings, if they are inheritable then we are talking potentially about a much bigger interference with the future gene pool. It is possible that what are regarded as genetic diseases today might be needed because of some advantage they would give in other circumstances. This might prove true particularly for some autosomal recessive diseases, where it takes two carriers mating to produce an offspring that has the characteristic that is deleterious and the carriers themselves may have an advantage. Thus far, of course, only sickle cell has been definitely identified this way, but there may be other advantages. Basically it doesn't seem that eliminating these genetic characteristics ought to harm the future. But making other changes which today seem desirable to us in the future may turn out to have been like shooting at a moving target.

If we think greater height is desirable, because people can then go out and be basketball players and make a lot of money, in 50 years it may turn out that is a terrible thing to have all these tall people around because we really ought to fit inside of spaceships and get shot up to the Moon to get away from the pollution.

The very fact that one has to make light of it just shows that you can't begin to predict the future that accurately. I don't think this thing ought to be entirely dismissed or physicians wouldn't go along with it. Already in the area of amniocentesis we see a few years ago, it was developed for the purpose of screening for serious genetic defects. Now we know that some parents are requesting and some physicians are willing to screen for fetal sex so as to allow parents to select for the sex of their child. It is a very small problem today.

Mr. GORE. And by select, you mean by aborting the fetus of a sex that is not preferred.

Mr. CAPRON. Right. Now it seems to us in the study that we did on genetic counseling and screening unlikely that that technique, which is fairly draconian, would be widely used by people today.

Mr. GORE. It certainly is allegedly widely used in China, for example.

Mr. CAPRON. I don't think they are using prenatal screening there but infanticide is alleged to be used.

Mr. GORE. And my information is that there is prenatal screening, not through amniocentesis but a related procedure and that it is used quite commonly for that purpose.

Mr. CAPRON. My purpose in mentioning amniocentesis was to show that there is something that was designed for the treatment, and in this case a treatment by deselection or avoidance by abortion of genetic problems, and some people said that this other use—sex selection—is the use we want to make of it.

Mr. GORE. Now, in looking at what we as a society ought to do, we ought to have a governmental body of the kind that you discussed with those characteristics to serve as a focal point for our collective awareness to look at these questions and problems and then we come to the question of possible prohibitions, one of which is in danger of being sensationalized. You discussed we may well have to have a prohibition on hybridization of humans, with other species. Should there be, also, a prohibition against the use of genetic engineering to enhance characteristics that are not related to the survival of the individual in question, but are just related to an individual parent's or doctor's whimsical choice about blond hair or blue eyes or tall stature?

In other words, should we consider giving this body, this governmental body the authority to compile and regularly update a list of applications that are permissible and prohibit use of these techniques for human applications that are not on that list?

Mr. CAPRON. Well, I think it may be surprising, but part of my concern with the notion of a govermental body is to avoid an overregulation in the field. If we look in the past at the abuses of genetic techniques, they are largely associated with governmental power. Even in our own country the passage of the genetic sterilization laws in the 1910's and 1920's was one of the things which held down the progress and the medical application of genetic knowledge for many years because of the bad name and justifiably so that that got. In some ways, prohibitions and Government control that you talked about, except in the most extreme cases, is troublesome, particularly ones which begin to differentiate between people who should be helped and those who shouldn't be helped. For a person with an IQ of 85 or 90, which doesn't prevent their surviving at all, to be told that, "we are not going to allow enhancement of intelligence so that you could function at a somewhat higher level" may seem as though the Government is really interfering in what would otherwise be a suitable, desirable medical treatment.

Now, I am not saying that any such treatment now exists. Obviously, it is the first thing that scientists would develop. But I would be as concerned about the potential effects of government regulations and the President's Commission talked about the first objective as being an educational objective and the second one as being one that is more out to make sure that the Federal Government and its agencies are prepared and are responding appropriately rather than regulating individual conduct.

There may, however, as you recognize, be some forms of genetic engineering that would go too far.

Mr. GORE. I know that the question that I asked and that is not a proposal, that is a question, conflicts with your understanding of what the ideal governmental body in this area would be. I am simply asking the question and perhaps as your answer indicates, you believe it is premature. I will ask other witnesses during the hearings about the question, but it seems to be at least possible at some point that an approach might be seriously considered.

Mr. CAPRON. I would expect that that would be best dealt with by having an individual case raised, as it were. If the body found particular research that was being designed to do something which it felt was very wrong then to focus attention on that and say, "this is something wrong" rather than in advance to say, "yes, one of the purposes of the body is to say you can have this and you can't have that." It was more the latter that I was referring to. I don't disagree that there may be questions when the body would face particular types of research and say this shouldn't be done.

Mr. GORE. Well, thank you for giving us an overview, Professor Capron. I took somewhat more time with you than we will take with most witnesses because you were presenting an overview and because the report which you have presented today is one that I believe is extremely important and signficant. We look forward to working with you closely in the future and many of the questions which you and the Commission have raised will inform the discussion which will take place here over the next 3 days.

So, again, congratulation on the work that you have done and thank you for appearing here today.

Mr. GORE. I would like to now call a panel of witnesses to the witness table, our panel on basic genetic engineering.

Dr. David Jackson, vice president and chief scientific officer of the Genex Corp.; Dr. Richard Axel, professor of biochemistry and pathology, Columbia University of Physicians and Surgeons; Dr. Barbara Sanford, director of the Jackson Laboratory, Bar Harbor, Maine; and Dr. Zsolt Harsanyi, vice president at E. F. Hutton & Co. If you would all come forward.

I would like to welcome all of you, some for not the first time. We certainly appreciate your willingness to come and share in this endeavor.

Without objection, the prepared statements of all our witnesses will be included into the hearing record in full at this point and I would like to ask Dr. David Jackson, vice president and chief scientific officer of the Genex Corp. if you would begin. Dr. Jackson, welcome.

STATEMENTS OF DAVID JACKSON, VICE PRESIDENT AND CHIEF SCIENTIFIC OFFICER, GENEX CORP., GAITHERSBURG, MD.; RICHARD AXEL, PROFESSOR OF BIOCHEMISTRY AND PATHOLOGY, COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS AND SURGEONS, NEW YORK, N.Y.; BARBARA SANFORD, DIRECTOR, JACKSON LABORATORY, BAR HARBOR, MAINE; AND ZSOLT HARSANYI, VICE PRESIDENT E. F. HUTTON & CO., INC., NEW YORK, N.Y.

Mr. JACKSON. Thank you, Mr. Chairman.

For the next 3 days, this subcommittee is going to be holding hearings on human applications of genetic engineering. Genetic engineering is a term which has gained great currency during the past 10 years, yet in spite of that, I think there is surprisingly little consensus about what it means, particularly in an operational sense. During the next several days, we will be discussing both what can and should or should not be done with such entities as genes, DNA molecules, chromosomes, genomes, and the like. We will hear a great deal, especially today, about how much progress has been made in the past few years in our ability to manipulate genes in very precise ways. It is certainly true that enormous progress has been made in our ability to manipulate some genes in some genetic contexts very precisely. It is equally true that many of the widely discussed applications of genetic engineering, especially many of the ones involving applications to humans, are of almost unimaginable complexity. They certainly cannot be done now. Moreover, it is unclear that they will be possible, let alone desireable from either a pragmatic or an ethical perspective, in the clearly foreseeable future.

In my testimony this morning, I will try to introduce you to this genetic universe, and to give you some sense for its vastness and complexity. I will also try to show you the small corner of it which we are now beginning to understand, while noting that this corner, though still tiny, is much larger than it was 10 years ago.

Genetic engineering involves working with DNA molecules. DNA molecules are of central importance in all living organisms where they perform two principal functions. Both functions depend on the fact that the entire heritable information of an organism—all of its genes—is stored in a kind of code in its DNA molecules. The first function of DNA is to transmit all of this information to the next generation of the organism, which the DNA does by duplicating itself and distributing identical copies to the progeny cells. The second function of DNA is to serve as the data base which is used to program all of the thousands of chemical reactions which must occur in living cells.

DNA molecules are long, stringlike molecules made up of only four different kinds of building blocks called A, C, G, and T. All the information stored in the DNA is contained in the sequence in which these four building blocks occur along the molecule. That is, the language of DNA is written with a four-letter alphabet. The sequence of building blocks in the DNA is converted into a sequence of similar building blocks in a related type of molecule called messenger RNA. The sequence of building blocks in the messenger RNA is in turn used to program the cellular machinery which makes enzymes or proteins. Enzymes are protein molecules which act as specific catalysts for the thousands of chemical reactions which occur in living cells.

In simple terms, a gene is that segment of a DNA molecule which codes for a single type of enzyme molecule. An average gene contains 1,500 to 2,000 of the building blocks. Even the simplest living organisms contain several thousand genes this size. The cells of the most complex organisms, such as man, contain approximately 1,000 times as much DNA as those of simple organisms such as bacteria. Another way of saying this is that if a typical gene is around 1,500 building blocks in length, then the simplest living organisms contain about 3 million building blocks' worth of DNA—all of it is in a single molecule composed only of A, G, C, and T—and the most complex organisms have about 3 billion building blocks in their DNA.

The complexity of this genetic material can be graphically appreciated by thinking of the DNA molecule as a piece of yarn, in which the yarn is about 100,000 times the size of the DNA molecule. On this scale, a typical gene is just over 2 inches long. On this same scale, the DNA content of the simplest microorganisms is about one-tenth of a mile of yarn. And the DNA content of a single human cell is equivalent to about 100 miles of yarn. To appreciate the genetic complexity of human DNA, imagine walking from Washington to Baltimore and back and seeing 15 to 20 new genes every step of the way, each one composed of about 1,500 building blocks smaller than the size of a period on a printed page.

I have emphasized the extraordinary genetic complexity of human DNA because that complexity, in and of itself, places several limits on what one could hope to accomplish with human genetic engineering.

As Professor Capron indicated, when one comes to a question of gene therapy, there are basically two classes of genetic engineering involving introduction of foreign DNA molecules into human cells to be considered.

These are what you referred to as the somatic and the germline approach. The first involves inserting "good" copies of a gene which is defective into a human embryo at an extremely early stage of development. Leaving aside the formidable problems of how to identify an embryo carrying a defective gene at such an early stage of development, I find it almost impossible to believe that the precision with which we can engineer something as complex as the DNA of human cells will be attained with a sufficiently high level of confidence that the procedure will be either ethically acceptable or pragmatically desirable. Recall that many genetic diseases are caused by a single incorrect building block out of the 3 billion or so in each cell.

The second type of genetic engineering involves attempting to cure individuals who have been diagnosed as having a genetic disease by some form of gene therapy. Here, too, there are formidable technical problems. In order to begin to work on a gene therapy approach to curing a genetic disease, the nature of the biochemical defect must in general be known.

Even if a good copy of the defective gene is in hand, there are major problems in introducing it into the target tissue, let alone to an adequate site inside the target cell where the disease is manifest. The major exception to this statement is genetic diseases of the blood, one of the few organs of the body which can be easily removed, manipulated in the laboratory at the cellular level and then reintroduced into the body. I wish to emphasize that in the foreseeable future genetic engineering is likely to require manipulation of human cells in the laboratory. It is possible that gene therapy may be developed for a few diseases of the blood, such as sickle cell anemia and thalassemia, during the next several decades. It is unlikely that similar success will be achieved for genetic diseases affecting other organs of the body.

Mr. **Gore**. What about at the embryonic stage?

Mr. **Jackson**. Well, the point I made earlier with respect to manipulation at the embryonic stage is that I think most people would agree that it would require extraordinary precision in order to make such manipulation ethically permissible. I think that level of precision is something we are unlikely to achieve rapidly, in part because of the tremendous genetic complexity which I tried to portray.

In spite of the generally bleak picture for gene therapy as a treatment for human genetic diseases, there are extremely promising and much less controversial ways in which genetic engineering is being successfully used to treat genetic diesases today. This approach is to use genetically engineered bacteria to synthesize the active human protein which is lacking in the individual afflicted with the genetic diseases. This approach has already been successfully applied to the treatment of congenital dwarfism and diabetes with the synthesis of human growth hormone and human insulin in genetically engineered bacteria. Additional human proteins with proven therapeutic potential for other genetic diseases are being developed in a variety of labs at the present time.

In closing, I wish to make one other point about the application of genetic engineering to human beings. A great deal of popular literature is based on the premise that it will soon be possible to use genetic engineering for directed manipulation—that is to say, manipulation where a predetermined result is sought and achieved—of complex characteristics such as intelligence, aggressiveness, personality, good looks, and so forth. All of these characteristics, to the extent that their determinants are genetic, are surely specified by many genes, none of which do we have the slightest clue at the present time as to how to identify biochemically. The idea that it will be possible to successfully and directly engineer such complex human traits in any foreseeable future is simply preposterous.

Earlier in my testimony, I used the metaphor of DNA as a language. Ten years ago, we had no effective ability to speak that language. Today we can read it, we can edit it, and increasingly we can write in the language of DNA. But I must emphasize that, relative to the fluency we would wish to have in this language, we are still at the preschool level. To successfully apply genetic engineering to human beings, we shall require a postgraduate degree in the language of DNA.

Thank you.

Mr. GORE. Postgraduate degrees from preschool usually take about 16 to 18 years. I hope you are right about it being preposterous and that it will not be possible, but most of our other witnesses have a different view of that. I am going to hold my questions though until the panel has been completed.

Mr. GORE. Dr. Richard Axel, professor of biochemistry and pathology, Columbia University of Physicians and Surgeons. Welcome.

Mr. AXEL. As we have just heard from Dr. Jackson, the human chromosome is complicated. It contains enough information to accommodate 10 million genes. The technology of recombinant DNA now permits us to isolate virtually any gene. Thus it is now possible for us to understand in great detail the molecular anatomy of individual genes which represent perhaps one-millionth of the human chromosome.

Simultaneously, techniques have now been developed which permit the stable introduction of genes into cells under conditions in which these screens frequently function correctly. Thus the fusion of these technologies, the ability to introduce virtually any cloned gene into any cell in the laboratory immediately raises the possibility of effective gene therapy in the treatment of genetic disorders in man.

What I wish to do briefly this morning is to discuss with you the techniques of gene transfer, the problems inherent in their performance, the prospects for their successful solution and the potential benefits which may be anticipated if, indeed, these problems can be solved.

Now the development of a successful regimen for gene therapy in the future requires the solution of several problems. First, procedures are required to efficiently introduce genes into cells with high efficiency. Second, the inserted gene must be stable within the cell such that it is not lost during the life of the cell which is frequently equivalent to the life of the organism.

Third, new introduced genes must synthesize the correct levels of gene product. Thus, the pattern of gene activity must mimic the pattern for a normal genes in normal cells.

Fourth, gene transfer must be performed at an appropriate time in development such that it is not already too late to correct the consequences of a mutation which may be apparent and irreversible in utero.

Finally, the introduction of genes into cells must not disrupt the normal functioning of other genes present within the chromosome of the recipient cell.

To understand these problems and the prospect for their successful solution, it is necessary to review briefly the recent development in the transfer of cloned genes. Let us begin with a discussion of the way in which DNA is introduced into cells. At the outset, it is important to emphasize that I will restrict my discussion to somatic cells. Cells of an organism may be broadly classified as somatic cells or gametes. Gametes ultimately develop into mature sperm or eggs and participate in the generation of offspring. The maximum life span of somatic cells equals the life span of an organism. Somatic cells die with the individual; the introduction of genes into somatic cells is therefore transient. The changes which are introdued into the genetic material are not propogated to offspring.

I think it is important to continue to reemphasize this point.

Mr. GORE. You would say that in terms of understanding the bioethical questions involved here that it is really a great divide? There is a very big difference between anything involving the somatic cells and anything that involes the germ line or gametes?

Mr. AXEL. Indeed both the prospect for successful solutions for the two sorts of therapy and the consequences are quite different.

Mr. GORE. And you are discussing the somatic cells?

Mr. AXEL. Yes.

Let's talk a bit about the technology.

When cultured cells are exposed to DNA, a small subpopulation of these cells stably integrate exogenous genes into their chromosomes in a form in which these genes are recognized by the enzymatic machinery of the cell. These genes are active, produce gene products, and can cure mutations in the recipient cell.

We may now consider these three technologies as a potential solution to the first problem posed above: Which procedure most effectively introduces a gene into cells with a high efficiency? The calcium phosphate precipitation procedure, at best, permits transfer to 1 percent of the exposed cell populations. In most genetic disorders, this is likely to be an inadequate frequency to compensate for genetic deficiencies. The second method, microinjection, permits a somewhat higher efficiency but is tedious, and although it is possible to inject several thousand cells, it is not feasible to inject the several million cells required for effective gene transfer in vivo. We are left, then, with the more recent and exciting possiblity of encapsidating DNA in viral coats such that all viral information has been removed, eliminating any potential harmful effects which may result from viral genes. This procedure, currently under development in a number of laboratories, is likely to provide a gene delivery system with an efficiency of 1; each cell exposed to DNA in a viral coat is likely to take up this DNA and integrate it into its chromosome. The problem of efficiency, thus, may soon be overcome.

We may next ask: What is the fate of DNA introduced into these cells by any of the three procedures? In each instance, the fate is similar. The DNA is almost always integrated into the chromosome of the recipient cell in such a form that it is stable for several generations. Thus, an exogenous gene introduced into the chromosome of a recipient cell is now transmitted to progeny cells at cell division. The problem of stability of newly inserted genes through the life of a cell and its propogation to daughter cells is effectively solved in each of the three procedures for gene transfer.

Let us consider the third problem, concerning the appropriate expression of newly introduced genes. In the organism, over 10,000 different genes are expressed, each demonstrating temporal and quantitative differences in the level of their expression. At different stages in development, or in response to different external stimuli, the level of activity of a given gene product can be changed to meet the changing requirements of an external environment.

Other genes are regulated differently. The levels of many genes remain constant throughout the life of a cell. A successful gene therapy regiment requires that the pattern of activity of newly inserted genes mimic that of a normal gene present within the chromosome of a normal cell. Consider in this regard a simple quantitative problem in the correction of a genetic disorder due to an enzymatic deficiency. Although it may be possible to insert a normal gene for an enzyme into a cell, too little activity will not be adequate to correct the deficiency.

On the other hand, overactivity may result in large quantities of specific gene products well beyond that observed in normal cells which may so disrupt the metabolism of the cell as to be lethal. Preliminary experimental evidence suggests that it will be possible to introduce genes into cells under conditions such that the level of the gene product will be adequate to correct the defect, but not so great as to correct new problems.

We turn now then to two final and enigmatic problems. When, during the development of an organism will gene therapy be most effective? In many disorders such as those involving the hemoglobins, it seems that early postnatal replacement could be adequate in curing these genetic deficiencies.

Other disorders including enzymatic deficiencies are frequently associated with anatomic defects that are not immediatley explained by the simple lack of an enzyme or by the simple genetic disorder. Are these changes evident in utero? Are they irreversible or reversible by subsequent postnatal gene therapy? Future work on lower animal models will have to provide these answers since they are currently unavailable.

Finally, we turn to the question of potential harm which may result from the fiscal insertion of a gene into the chromosome. I can envisage potential problems which may result from the introduction of DNA at random locations within the cells' chromosomes. Although unlikely, it remains possible that new introduced genetic information may be inserted into an essential region of the chromosome and in this way disrupt the function of a preexisting gene resulting in the death of a cell. This remains a potential problem for which solutions must be obtained before gene therapy can be anticipated.

What are the prospects that these five problems can be solved in the near future, thus permitting the development of a successful regimen of gene therapy? The solution to the problem of the efficiency of the gene transfer is well underway by utilizing viral encapsulation of cloned genes. If genes may ultimately be inserted into appropriate locations within the chromosome, they will be stable. They are likely to maintain appropriate levels of activity and will not disrupt other essential genes. Thus none of the problems inherent in the development of a successful gene therapy prevents an insurmountable experimental barrier. Many have been overcome and the remainder, I anticipate will likely soon be solved by continued experimentation in similar systems.

You may now reasonably ask, then, with this background, what specific disorders can be most appropiately approached by this sort of gene therapy? Several hundred inherited enzymatic deficiencies have been identified for which effective therapy is unavailable. Many of these disorders may be corrected by gene transfer. It should be emphasized, however, that gene transfer of somatic cells is technically limited to experimentally accessible compartments of cells. For this reason, I do not anticipate successful gene transfer into the nervous system or into the skin, for that matter, in the near future.

On the other hand, cellular compartments, such as the bone marrow are readily accessible to therapy and can be removed and reintroduced into the organism following gene insertion.

One specific disorder which may provide a good candidate for initial attempts at gene therapy is a disorder known as severe combined amino deficiencies caused by the lack of one of two enzymes. In this disorder, the clinical syndrome emerges in which the immune system is severely impaired. The immunity defect is frequently apparent at 1 to 2 months of age and involves a clinical picture of recurrent infections which is progressive and frequently results in death from infectious agents that are not pathogenic in normal individuals. Afflicted cells reside in the bone marrow and accessible compartments. Further, the enzyme required to detect the defect is required at low levels throughout the life of the cell. Thus genetic correction of this defect would restore to the bone marrow competent population of immune cells. This disorder, therefore, provides a likely initial candidate for attempts at gene therapy to correct a uniformly fatal disease.

Let me consider for a moment defects in more complex genes responsible for a variety of other disorders. A host of different genetic effects afflict two hemoglobin genes. As we have heard and will hear, the hemoglobin genes are finally regulated during development. Their activity is required in abundance to fulfill the oxygen delivery needs of the organism. The globin genes, therefore, are difficult to regulate correctly—they are fastidious genes. I anticipate that while effective gene therapy for these disorders may ultimately be developed, problems inherent in such a fastidiously controlled set of genes will require continued expermimentation before effective gene therapy can be anticipated.

Finally, the idea of introducing genes into humans has conjured up, as we have heard, frightening and frequently unnatural scenarios which derive largely and too often from fantasy. Recall that I have restricted my discussion to the introduction of genes into somatic cells, cells which die with the individual such that changes introduced into the gentic material of these cells is not propagated to offspring.

We are dealing, therefore, in this discussion with the therapy of life-threatening disorders effective in a single individual for a single generation. Such a scenario does not, for me, create ethical problems. On the contrary, it would seem as we have heard, unethical not to apply this exciting new information and new capabilities to eliminate the clinical systems of genetic disorders.

Thank you.

[The prepared statement of Richard Axel follows:]

Gene Transfer and Gene Therapy

Dr. Richard Axel

Columbia University, College of Physicians and Surgeons

The technology of recombinant DNA now permits the isolation of virtually any animal cell gene. The analysis of the fine structure of a gene utilizing rapid sequencing techniques allows a detailed look at the molecular anatomy of single genes which represent perhaps one-millionth of the human genetic material or the human chromosome. Simultaneously, techniques have been developed which permit the stable introduction of genes into cells under defined culture conditions. The ability to introduce virtually any cloned gene into any somatic cell immediately raises the possibility of effective gene therapy for genetic disorders of man.

The development of a successful regimen for gene therapy in the future requires the solution of several problems. First, procedures are required to introduce genes into cells with high frequency such that a significant percentage of a population of cells has received the new gene. Second, the inserted gene must be stable within the recipient cell such that it is not lost at high frequency during the life of the cell, which is frequently equivalent to the life of the organism. Third, expression of donor genes must be appropriately regulated to generate the correct levels of gene product at appropriate times. Thus, the pattern of gene expression must mimic the pattern observed for the gene in normal cells. Fourth, gene transfer must be performed at the appropriate developmental time such that it is not already too late to correct the consequences of a mutation which may be apparent and irreversible in utero. Finally, the introduction of genes into cells must not disrupt the normal functioning of endogenous genes present within the chromosome of the recipient cell.

To understand these problems and the prospect for their successful solution, it is necessary to review the recent developments in the transfer of cloned genes. Let us begin with a discussion of the way in which DNA may be introduced into cells. At the outset, it is important to emphasize that I will restrict my discussion to somatic cells. Cells of an organism may be broadly classified as somatic cells or gametes. Gametes ultimately develop into mature sperm or eggs and participate in the generation of offspring. The maximum life span of somatic cells equals the life span of an organism. Somatic cells die with the individual; the introduction of genes into somatic cells is therefore transient. The changes which are introduced into the genetic material are not propogated to offspring.

When cultured cells are exposed to DNA, a small subpopulation of these cells stably integrate exogenous genes into their chromosomes in a form in which these genes are recognized by the enzymatic machinery of the host cell. These genes are expressed, produce gene products, and can cure mutations in the recipient cell. At present, there are three major routes of gene transfer, each with inherent advantages depending on the object of study. Historically, the first and simplest method for effecting DNA-mediated gene transfer involves the formation of a co-precipitate between DNA and the compound calcium phosphate. When this precipitate is exposed to cells, a small population of cells will envelop the precipitate and incorporate the DNA into its chromosome where it behaves in many ways like an ordinary cellular gene. A second direct approach to gene transfer simply involves the use of microneedles to inject genes directly into the nucleus of specific cells.

Finally, recent developments permit the encapsidation of specific genes within virus coats free of potentially harmful viral genetic information. Cells exposed to encapsulated DNA efficiently incorporate this DNA into their chromosomes.

We may now consider these three technologies as a potential solution to the first problem posed above: Which procedure most effectively introduces a gene into cells with a high efficiency? The calcium phosphate precipitation procedure, at best, permits transfer to 1% of the exposed cell populations. In most genetic disorders, this is likely to be an inadequate frequency to compensate for genetic deficiencies. The second method, microinjection, permits a somewhat higher efficiency but is tedious, and although it is possible to inject several thousand cells, it is not feasible to inject the several million cells required for effective gene transfer in vivo. We are left, then, with the more recent and exciting possibility of encapsidating DNA in viral coats such that all viral information has been removed, eliminating any potential harmful effects which may result from viral genes. This procedure, currently under development in a number of laboratories, is likely to provide a gene delivery system with an efficiency of 1; each cell exposed to DNA in a viral coat is likely to take up this DNA and integrate it into its chromosome. The problem of efficiency, thus, may soon be overcome.

We may next ask: What is the fate of DNA introduced into these cells by any of the three procedures? In each instance, the fate is similar. The DNA is almost always integrated into the chromosome of the recipient cell in such a form that it is stable for several generations. Thus, an exogenous gene introduced into the chromosome of a recipient cell is now transmitted to progeny cells at cell division. The problem of stability of newly inserted genes through the life of a cell and its propogation to daughter cells is effectively solved in each of the three procedures for gene transfer.

The solution, however, is an imperfect one. In each chromosome, each endogenous gene has a distinct and stable position. The position of a gene is thought, at least in part, to regulate its expression. All current gene transfer procedures in cells of higher organisms do not permit the introduction of genes at their appropriate location in the chromosome. For example, it is possible to introduce a normal B-globin gene into a cell bearing mutant B-globin genes (genes responsible for the production of hemoglobin), but the newly introduced genes will reside at a location different from that of the endogenous mutant genes. It is the ultimate goal of a number of investigations to introduce genes at their homologous or appropriate loci within the chromosome, but to date this has not been effected.

Let us consider the third problem, concerning the appropriate expression of newly introduced genes. In the organism, over 10,000 different genes are expressed, each demonstrating temporal and quantitative differences in the level of their expression. At different stages in development, or in response to different external stimuli, the level of a given gene product can be changed to meet the changing requirements of an external environment. For other genes, known as constitutive genes, the levels of expression largely remain constant throughout the life of a cell. A successful gene transfer regimen requires that the pattern of expression of newly inserted genes mimic that of a normal endogenous gene present within the chromosome of a normal cell.

Consider a simple quantitative problem in the correction of a genetic disorder due to an enzymatic deficiency. Although it may be possible to insert a normal gene encoding this enzyme into a cell, too little expression will not be adequate to correct the deficiency. On the other hand, overexpression may result in large quantities of a specific gene product well beyond that observed in normal cells which may so disrupt the metabolism of a cell as to be lethal. Similarly, we must consider problems of temporal control of gene expression. The generation of a mature red cell replete with hemoglobin, which serves to carry oxygen to peripheral tissues, follows a precise time-dependent developmental pathway. The pathway occurs in the bone marrow, and very late in the maturation of this cell, hemoglobin is produced immediately prior to the release of these cells into the blood stream. If hemoglobin were produced early in the maturation process, the cells in the bone marrow but not the peripheral blood would be full of this oxygen carrying potential. Thus, the timing of expression of newly inserted genes is an important parameter which must mirror the timing observed in normal cells of the organism.

In very preliminary studies utilizing genes whose expression is temporally controlled, the timing of gene expression during development mimics that observed for normal cells. Thus, preliminary experimental evidence suggests that it will be possible to introduce genes into cells under conditions such that the level of the gene product will be adequate to correct the defect, but not so great as to create new problems, and further, the timing of expression may be appropriate for the specific gene in the specific cell.

We turn now to two final and most enigmatic problems. When in developmental time will gene transfer be most effective? In disorders which involve the inappropriate expression or the expression of mutant hemoglobins, it is apparent that early post-natal replacement could be adequate in curing these genetic deficiencies. Other disorders, such as enzymatic deficiencies in amino acid, lipid or purine metabolism are frequently associated with anatomic and mental defects that are not immediately explained by the simple enzymatic defect. Are these changes evident *in utero*, are they irreversible or are they reversible by subsequent post-natal gene replacement therapy? Significant work in model systems involving cultured cells and, ultimately, lower animal models, may provide answers to these questions which are currently unavailable.

Finally, we turn to the question of potential physical harm which may result from the act of insertion of a gene into the chromosome. We can envisage potential problems which may result from the introduction of DNA at random locations within the cells' chromosomes. Although unlikely, it remains possible, at present, that newly introduced genetic material may insert into an essential region of the chromosome, thus disrupting the function of a pre-existing gene, resulting in the death of a cell. It is also possible that newly introduced genes may produce an overabundance of an essential gene product, thus disrupting the normal metabolism of a cell.

The use of gene transfer has for the most part been restricted to cells in tissue culture. Recent advances will now permit rapid experimentation in animal model systems in vivo in which the effect of transfer on individual cells within the organism, and on the organism as a whole, may be investigated in greater detail. Clearly, answers to this problem, the problem of potential harm to other functioning genetic systems within the cell, must be answered before any attempts at gene therapy can be anticipated in humans.

What are the prospects that these five problems can be solved in the near future, thus permitting the development of a successful regimen of gene therapy? The solution to the problem of the efficiency of gene transfer is well underway by utilizing viral encapsidation of cloned genes. If genes may ultimately be inserted into their appropriate endogenous location within the chromosome, they will remain stable, are likely to be appropriately expressed, and are likely not to disrupt other essential genes. I anticipate that by continued experimentation and the rapid development of animal model systems these problems will be overcome. None of these problems present an insurmountable barrier and many have been overcome in similar gene transfer systems in lower organisms such as yeast and bacteria. This area of investigation requires continued support.

We may now reasonably ask what specific disorders can be most appropriately addressed by this sort of gene therapy. Several hundred inherited enzymatic deficiencies have been identified for which effective therapy is unavailable. The deficiency of a specific enzyme results either in the accumulation of toxic products or the absence of essential products of the enzymatic reaction. These disorders involve carbohydrate metabolism, amino acid metabolism, lipid metabolism, steroid metabolism, and in each instance may be correctable by effective gene transfer. It should be recalled, however, that gene transfer in somatic cells, at present, is technically limited to accessible compartments of cells. I do not anticipate successful gene transfer into the nervous system or into the skin, for that matter, in the near future. On the other hand, cellular compartments such as the bone marrow are readily accessible to manipulation by the removal of marrow cells and subsequent reintroduction into the organism following gene insertion technologies. One important requirement for initial gene therapy is that it be adequate to insert genes, deficient in all cells in the organism, into a limited subpopulation of cells such that this subpopulation of cells may ultimately express levels of gene product necessary to correct the deficiency. In many instances, the answer to this problem is at present unknown due to the absence of appropriate animal model systems which mimic the host of human disorders catalogued to date. It should be noted, however, that the ability to perform gene transfer procedures in animal model systems will serve to create models of inherited disease not possible prior to the development of this sort of technology.

One disorder which may provide a good candidate for initial attempts at gene therapy are the immunodeficiency diseases caused by adenosine deaminase deficiency and purine nucleoside phosphorylase deficiency. The development of efficient immunity requires the participation of several different cell types including the T and B lymphocytes. In the disorder noted above, severe combined immunodeficiency disease, SCID, a clinical syndrome emerges in which both cellular and humoral immunity are severely impaired. The immune defect is frequently apparent at one to two months of age, and involves a clinical picture of recurrent infection, which is progressive and frequently results in death from infectious agents that are not usually pathogenic in normal individuals. Disease may result from a deficiency in either adenosine deaminase or purine nucleoside phosphorylase, enzymes involved in the degradation of nucleic acid precursors. The pathogenesis of this disorder is thought to result at least in part from the accumulation of toxic products. Afflicted cells reside in the marrow, an accessible compartment. Further, the enzyme required to correct the defect is required at low and constant levels and is maintained at a virtually identical level throughout the life of the cell. It is thought that the toxic products are harmful or lethal to immune cells. Thus, genetic correction of the defect would confer upon cells which efficiently express a newly inserted gene a selective growth advantage, thus restoring to the marrow a competent population of immune cells. Numerous investigators are in the process of isolating the genes encoding these enzymes and this disorder seems for many reasons a likely initial candidate for attempts at gene therapy to correct this uniformly fatal disease.

Let us consider defects in more complex genes responsible in a variety of genetic disorders. A host of different genetic defects afflict the globin genes. As noted previously, the globin genes are finely regulated in developmental time. Further, their expression is required in abundance to fulfill the oxygen delivery needs of the organism. We may consider the globin genes as a fastidious set of genes in their regulation. We anticipate that while effective gene therapy for these disorders may ultimately be developed, the problems inherent in such a fastidiously regulated set of genes will require continued additional investigation before we can anticipate effective gene therapy.

Finally, it is perhaps worth noting that the idea of introducing genes into humans has conjured up frightening and unnatural scenarios. Recall that I have restricted my discussion to the introduction of genes into somatic cells, cells which die with the individual, such that changes introduced into the genetic material of these cells is not propogated to offspring. We are dealing, therefore, with the therapy of life-threatening disorders effective in a single individual for a single generation. Such a scenario does not create ethical problems. Given a solution to the problems inherent in the development of a successful gene therapy regimen, it would simply be unethical not to employ it to effectively eliminate clinical symptoms of numerous genetic diseases.

Mr. **Gore**. Thank you very much. Again, we will hold questions.

Dr. Barbara Sanford, director of the Jackson Laboratory at Bar Harbor, Maine. Welcome

Mr. **Jackson**. Thank you.

Ms. **Sanford**. Thank you. The rapid advances in molecular biology of the past 10 years have opened up new approaches to the study of mammalian genetics and developmental biology. Genes can now be cloned, their biochemical structure can be determined using rapid sequencing methods, the genetic constitution of cultured mammalian cells can be altered by introduction of new DNA and DNA can be introduced directly into the nuclei of somatic cells or of fertilized eggs.

This scientific and technical progress has profoundly broadened our understanding of the structure and functions of genes. It has given us hope for developing new approaches to cancer and to genetically transmitted defects and diseases. And perhaps most important, each advance in this rapidly moving area opens up additional questions which stimulate further research on the mechanisms underlying both normal and abnormal development and differentiation.

By focusing attention on some representative current experiments involving investigators at the Jackson Laboratory, I would like to point out some of the advances being made in genetic engineering. I also want to stress my conviction that much more research on genetic mechanisms needs to be undertaken in animal models before gene transfer should be considered as a clinical approach to treatment of human disease.

One example using the new technology is the work of Drs. Thomas E. Wagner of Ohio State University, Peter C. Hoppe of the Jackson Laboratory and their associates. Just over a year ago, these investigators reported the successful introduction of a rabbit globin gene, the gene for beta globin—a component of hemoglobin—into fertilized mouse eggs.

I have a few slides. Do you want to see them?

Mr. GORE. Yes. We had some slides and films at earlier hearings. I think it is helpful to look at exactly how the procedure is done.

Dr. SANFORD. This gives you an example of the microinjection procedure. As you can see, there is a very tiny micropipette that is about the size of a human hair. Through that micropipette, the investigator will be injecting DNA of a rabbit beta globin gene into the nucleus which was contributed by the sperm. This is a very recently fertilized egg, and the sperm and the egg nucleus are still separate. Here you see the basic procedure for introducing the new DNA from the rabbit into the pronucleus or sperm nucleus of the fertilized mouse egg.

The next slide shows you the design of the Wagner-Hoppe experiment. On the left you see the rabbit beta globin gene or gene fragment, being combined with a plasmid, and then being injected into the sperm nucleus.

After the microinjection of the DNA, the next step is for the eggs which came from that mouse you see——

Mr. GORE. Yes; go ahead.

Dr. SANFORD. On the right-hand corner of the slide you see the female mouse from whom the eggs are derived. And you see below that, a representation of the microinjection process with the injection of the rabbit DNA into the mouse sperm nucleus.

The eggs are then grown for 5 days in culture, and the embryos which develop are transplanted to foster mothers. As a result of injecting 312 fertilized eggs, 46 offspring were born.

The expression of the rabbit gene was demonstrated by identifying rabbit beta globin in the blood of 5 of the 46 mice which had been injected with the rabbit DNA. Two of the mice which expressed the rabbit globin gene were mated and it was found that all five of their tested offspring also produced the rabbit beta globin. This experiment showed that genes can be introduced into a zygote, function in the adult and be passed through the germ line on to the next generation.

These are exciting findings. But as the investigators who were involved have pointed out, more research will be required to determine the stability of the rabbit beta globin gene in recipient mice and their offspring.

There are many examples in humans and in laboratory animals of disorders which are transmitted by single mutant genes. Over 700 mouse mutants which mimic human diseases have been found to date, and over 200 of these have been characterized and are being maintained at the Jackson Laboratory.

On this slide, you see a partial list of such mutants. There are, for example 89, different known mutations affecting the immune system. One of these is called wasted, and results in a mouse which is pathologically and physiologically similar to patients with ataxia telangiectasia.

A logical extension of the research I described earlier is the introduction of DNA from a normal gene into an experimental animal with a defect due to a single mutant gene. One example of this type of approach is the work now being carried out at the Jackson Laboratory in a collaborative project involving Drs. Jane E. Barker, Edward H. Birkenmeier, and Peter C. Hoppe.

Their experiments provide some insight into potential biological complications of attempts to correct genetic disease by gene transfer. They are working with a mouse model for alpha thalassemia, a genetically determined human anemia particularly common in Asian countries. This type of anemia is caused both in mouse and man by a deficiency in the alpha globin component of hemoglobin.

Essentially the same microinjection technique is used as in the previously described experiment. The male pronuclei in fertilized eggs from thalassemic mice are injected with human alpha globin genes in plasmid vectors or carriers. In some cases, an additional viral component, a long terminal repeat from a retrovirus, is injected along with the human gene in an attempt to promote recombination and integration of the genetic material.

After the microinjection process, the fertilized eggs are cultured and then are transferred to foster mothers to complete their development. When the mice reach adulthood, blood tests are done to see whether or not they are thalassemic, and the DNA from their spleens is studied for evidence of integration of the transferred genetic material into the mouse genome.

The first 21 mice studied have shown no significant variation from the expected ratio of normal to affected offspring. No alterations in blood values from that expected were found in either normal or thalassemic mice which had been microinjected.

On the other hand, analysis of DNA content in the spleens of these mice produced evidence that two mice, neither of which carried thalassemia, had incorporated microinjected DNA into their genomes. In one case, both the plasmid vector and the human alpha globin gene were found to be present. Ten of the eighty progeny of this mouse have been tested to date and, although half show the presence of the plasmid, none of the progeny has incorporated the human alpha globin gene.

In the other case, a male recipient which was not thalassemic lost a DNA sequence similar to that of the alpha globin gene. Mating this male with one of his daughters produced severely anemic offspring which died before birth. Studies are currently underway to determine the basis for this abnormality.

The results of these experiments to date underscore the fact that simply injecting genetic material does not assure its expression. The results also evoke concern that, under some conditions, gene transfer may produce genetic damage. This of course comes as no surprise to geneticists who are accustomed to dealing with complicated questions involving gene action.

The research I have described illustrates both the promise and the problems associated with the use of recombinant DNA technology in experimental genetics, and ultimately in the treatment of human disease. Although successful transfers of genetic material and even germ line transmission of transferred genes have been achieved, many problems remain:

Transferred genes must be correctly transcribed into messenger RNA and translated into protein to be effective, and more information is needed about these steps.

We must learn more about the organization of mammalian genes. It may well be critical that some genes be integrated into chromosomes at specific sites rather than in a random manner. A hopeful note here is the work of Dr. Rubin and his colleagues in drosophila where it has been possible to transmit material directly to specific sites on the chromosome using transposons.

Overall, we have little understanding at this time of how mammalian gene expression is controlled; that is, how gene action is regulated and coordinated during development. The fact that introduction of new genes is more easily accomplished than expression of these genes was one of the main points emphasized at a recent workshop on gene transfer conducted at NIH.

Clearly there is a need to gain understanding in each of these areas before we apply these new techniques effectively to the treatment of human disorders. I am confident that basic scientists, working with cells in culture and in animal models, will successfully confront these problems and that the future therapeutic applications of genetic engineering will benefit us all.

I welcome the interest of your subcommittee, Mr. Chairman, and look forward to the results of your deliberations.

Thank you very much.

[The prepared statement, plus attachments of Dr. Sanford follow:]

TESTIMONY OF
DR. BARBARA H. SANFORD, DIRECTOR
THE JACKSON LABORATORY

SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT
COMMITTEE ON SCIENCE AND TECHNOLOGY
U. S. HOUSE OF REPRESENTATIVES
NOVEMBER 16, 1982

Mr. Chairman and Members of the Subcommittee:

The rapid advances in molecular biology of the past 10 years have opened up a number of new approaches to the study of mammalian genetics and developmental biology. Mammalian genes can now be cloned (1-3); their biochemical structure can be determined using rapid sequencing methods (4,5); the genetic constitution of cultured mammalian cells can be altered by introduction of new DNA (6); and DNA can be introduced directly into the nuclei of somatic cells (7-8) or of fertilized eggs (9-13).

This scientific and technical progress has profoundly broadened our understanding of the structure and functions of genes. It has given us hope for developing new approaches to cancer and to genetically transmitted defects and diseases. And perhaps most important, each advance in this rapidly moving area opens up additional questions which stimulate further research on the mechanisms underlying both normal and abnormal development and differentiation.

By focusing attention on some representative current experiments involving investigators at the Jackson Laboratory, I would like to point out some of the advances being made in genetic engineering. I also want to stress my conviction that much more research on genetic mechanisms needs to be undertaken in animal models before gene transfer should be considered as a clinical approach to treatment of human disease.

One example using the new technology is the work of Drs. Thomas E. Wagner of Ohio State University, Peter C. Hoppe of the Jackson Laboratory and their associates (14). Just over a year ago, these investigators reported the successful introduction of a rabbit globin gene, the gene for β globin (a component of hemoglobin) into fertilized mouse eggs. The experiment was carried out as follows:

1. Using a micropipette (external diameter 1-2 μm) E. coli plasmids containing DNA coding for rabbit β globin were injected into the male pronuclei of 312 fertilized mouse eggs (Illustration 1 shows the process of microinjection of DNA into the male pronucleus of the fertilized mouse egg. Illustration 2 shows the design of the experiment).

2. After microinjection, the eggs were grown for 5 days in culture tubes. Two hundred and eleven embryos developed in culture and were transplanted to foster mothers. As a result, 46 offspring were born.

3. The expression of the rabbit gene in the mice was demonstrated by testing these mice as adults and identifying rabbit β globin in the hemoglobin of 5 of the 46 mice which had been injected with the rabbit DNA.

4. Two of the mice expressing the rabbit globin gene were mated and it was found that 5 of their tested offspring also produced the rabbit β globin. This result indicated that the microinjected DNA was integrated into the parent's genome and transmitted to the next generation.

This experiment showed that the expression of a genetically controlled trait could be permanently altered by transfer of genetic material from another individual early in development and that the genetic change induced could be transmitted to the offspring. These are exciting findings, but as the investigators involved have pointed out more research will be required to determine the stability, integration and expression of the rabbit β globin gene in recipient animals and their offspring.

There are many examples in laboratory animals of diseases transmitted by single mutant genes. At the Jackson Laboratory, we have been identifying and characterizing such mutations in the mouse for many years. Illustration 3 gives a partial list of such mutants. These mutants often serve as good models of human diseases, and should help us develop approaches to gene therapy for some of our most serious health problems.

A logical extension of the research I have just described is the introduction of DNA from a normal gene into an experimental animal with a defect due to a single mutant gene. One example of this type of approach is the work now being carried out at the Jackson Laboratory in a collaborative project involving Drs. Jane E. Barker, Edward H. Birkenmeier and Peter C. Hoppe (16). Their experiments provide some insight into potential biological complications of attempts to correct genetic diseases by gene transfer. They are working with a mouse model for alpha thalassemia, a genetically determined human anemia particularly common in Mediterranean countries. This type of anemia is caused by a deficiency in the alpha globin component of hemoglobin (Illustration 4 shows the design of the experiments).

In these experiments, fertilized eggs from thalassemic mice are injected with a human alpha globin gene in a plasmid vector (pBR322). In some cases a viral component (a long terminal repeat from a retrovirus) is connected to the injected human gene in an attempt to promote recomination and integration of the genetic material.

After the microinjection process, the fertilized eggs are cultured and then are transferred to foster mothers to complete their development. When the mice reach adulthood, blood tests are done to see whether or not they are thalassemic, and the DNA from their spleens is studied for evidence of integration of the transferred genetic material into the mouse genome.

The first 25 mice studied have shown no significant variation from the expected ratio of normal to affected offspring. No alterations in blood values from that expected were found in either normal or thalassemic mice which had been microinjected.

On the other hand, analysis of DNA content in the livers of these mice produced evidence that two mice, neither of which carried thalassemia, had incorporated microinjected DNA into their genomes. In one case, both the plasmid and the human alpha globin gene were found to be present. Ten of the 80 progeny of this mouse have been tested to date and, although half show the presence of the plasmid, none of the progeny has incorporated the human alpha globin gene.

In the other case, a male recipient which was not thalassemic lost one of his own pseudo-alpha globin genes. Mating this male with some of his daughters produced severely anemic offspring which died before birth. Studies are currently underway to determine the basis for this abnormality.

The results of these experiments to date underscore the fact that simply injecting genetic material does not assure its expression. The results also evoke concern that, under some conditions, gene transfer may produce genetic damage. This, of course, comes as no surprise to geneticists who are accustomed to dealing with complicated questions involving gene action.

The research I have described illustrates both the promise and the problems associated with the use of recombinant DNA technology in experimental genetics, and ultimately, in the treatment of human disease. Although successful transfers of genetic material and even germ line transmission of transferred genes have been achieved, many problems remain:

-- Transferred genes must be correctly transcribed and translated to be effective, and more information is needed about these steps.

-- We must learn more about the organization of mammalian genes. It may well be critical that some genes be integrated into chromosomes at specific sites rather than in a random manner.

Overall, we have little understanding at this time of how mammalian gene expression is controlled; that is, how gene action is regulated and coordinated during development. The fact that introduction of new genes is much more easily accomplished than expression of these genes was one of the main points emphasized at a recent workshop on gene transfer conducted at NIH (17).

Clearly, there is a need to gain understanding in each of these areas before we apply these new techniques to the treatment of human disorders. I am confident that basic scientists, working with animal models, will successfully confront these problems and that the future applications of genetic engineering will benefit us all. I welcome the interest of your subcommittee, Mr. Chairman, and look forward to the results of your deliberations.

ILLUSTRATION 1

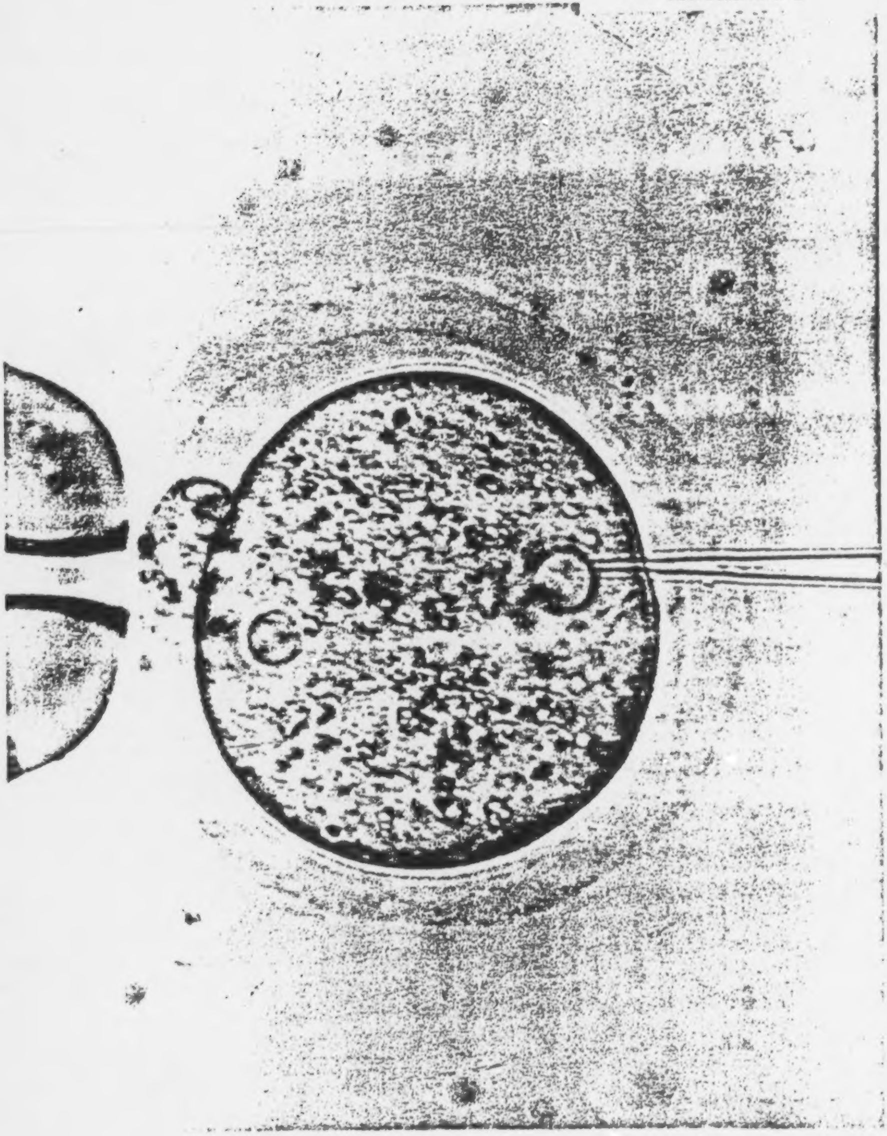
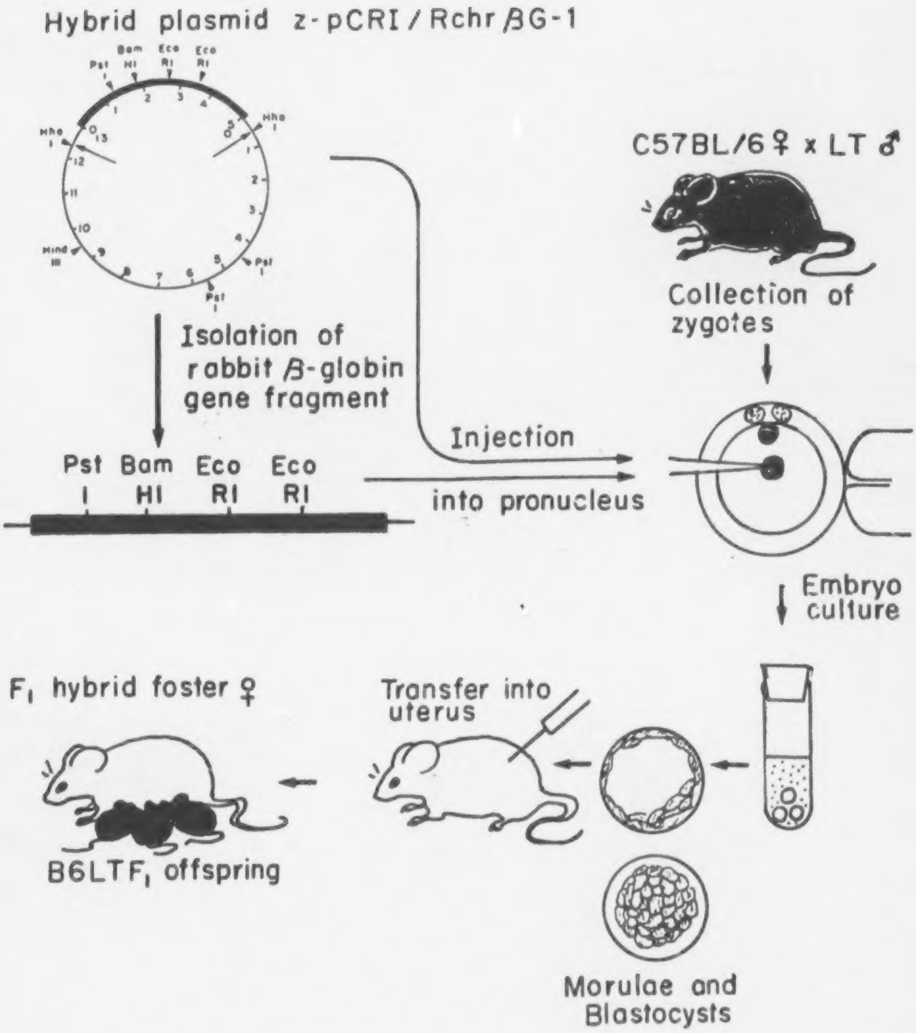


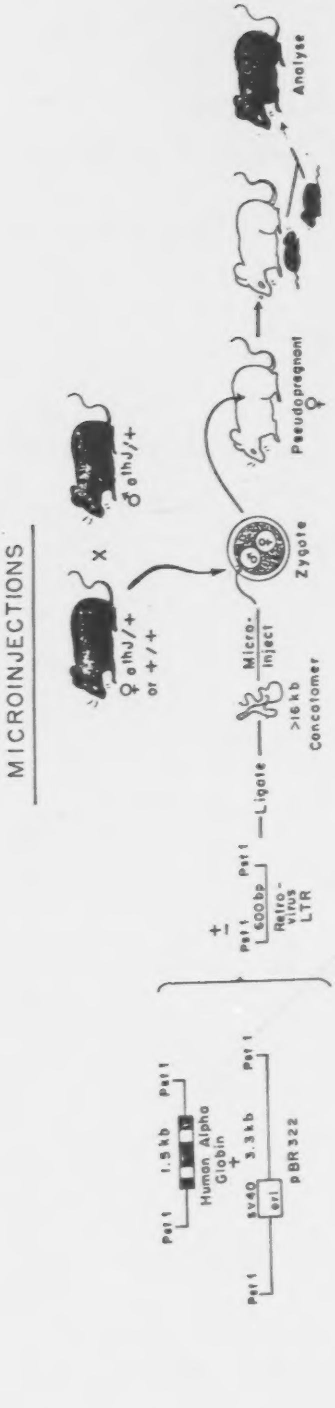
ILLUSTRATION 2


Hybrid plasmid z-pCRI/RchrβG-1
Pst I
Bam HI
Eco RI
Eco RI
Hha I
Hha I
Hind III
Pst I
Pst I
0
1
2
3
4
5
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Isolation of rabbit β-globin gene fragment
Pst I
Bam HI
Eco RI
Eco RI
Injection
into pronucleus
C57BL/6 ♀ x LT ♂
Collection of zygotes
Embryo culture
Morulae and Blastocysts
Transfer into uterus
F₁ hybrid foster ♀
B6LTF₁ offspring

MOUSE MUTANTS AS MODELS OF HUMAN DISEASES

System Affected	No. of Different Mouse Mutants	Examples	Similar to Human Defects
Pigment	57	*Mo*	Menke's syndrome
Skeleton	88	*Ph*	Cleft palate
Eye	41	*rd*	Retinal degeneration
Neurological	72	*twi*	Krabbe's syndrome
Blood	18	*an*	Fanconi's anemia
Endocrine	28	*db* *Hyp*	Diabetes Vitamin D resistant rickets
Reproductive	25	*Tfm*	Testicular feminization
Immune	89	*wst*	Ataxia telangectasia
Muscle	2	*mto*	Classical myotonia

ILLUSTRATION 4


MICROINJECTIONS
♀ a^thJ/+
or +/+
×
♂ a^thJ/+
Pst1
1.5kb
Pst1
Human Alpha
Globin
+
Pst1
SV40
ori
3.3kb
Pst1
pBR322
±
Pst1
600bp
Pst1
Retro-
virus
LTR
—Ligate—
>16 kb
Concatomer
Micro-
inject
♂
♀
Zygote
Pseudopregnant
♀
Analyse

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Mr. GORE. Our final witness on this panel is Dr. Zsolt Harsanyi, vice president of D&A Sciences at the E. F. Hutton Co. and someone who is familiar to this subcommittee, and formerly directed the OTA landmark study in this area.

We welcome you again on this occasion.

Dr. HARSANYI. Thank you very much, Mr. Chairman.

Instead of reading the testimony which I have provided the committee with, I will summarize it for you so that I don't duplicate anything that has been said already.

But before I do so, I would like to start off with a general statement as to what the thesis of my presentation is, and that is that the terminology that we use in this area is of extreme importance, particularly for the public that would be looking at this technology in the future, and of course legislators who will be looking at it.

As an example, I will remind you of what was brought up earlier this morning when Professor Capron talked about the National Science Foundation study, and when you picked up on that two-thirds figure that the public is against genetic engineering—I would like to remind the committee that in fact the words that were used in the questionnaire, if I recall, were something to the effect that people are afraid of the actual—if I can recall the exact words, and these were the critical words—alteration of human life forms or creating new life forms.

So the question was, do you approve of research that leads to the formation of new life forms?

Now, put that way, I am sure a lot of people immediately conjure up images of the "Creature from the Black Lagoon" or "Frankenstein," but not about penicillium strains that produce more antibiotics. Both of those situations would be under the same heading, the alteration or creation of new life forms, in that general sense.

If somebody had simply asked the question a different way, are you against the use of or the introduction of a single gene to repair a defect among 100,000 genes, perhaps the answer of the public or the answers of the public would have been different. So I think the terminology is extremely important.

Mr. GORE. Let me say that scientists are not the only profession that has difficulty with polling questions.

Dr. HARSANYI. If I might, I will also mention one anecdote in this area.

While I was at OTA, an attorney called me up from a town council meeting and told me about a situation where the town council was worried about the potential transfer of this human genetic information, mixing it between monkeys and other lower animal species. And the town council did in fact pass a resolution that they will ban in the city limits any transfer of human genetic material until someone realized what that meant.

You can imagine they soon changed that.

Mr. GORE. You do have to be precise, don't you?

Dr. HARSANYI. Right. But to get to the point, then, what I would like to summarize is simply this: When we talk about genetic engineering, I think we have to really talk about four different kinds of genetic engineering. And the reason for this is not only because the time for when they will become technical realities will differ considerably, but also because of the ethical and sociological implications of the use of these various techniques.

They have been referred to and alluded to several times today. But let me summarize them.

First, we can make a division in terms of the timing of when the actual manipulation would take place, and we can have the two groups, either prenatally or postnatally. So we can start talking about genetic engineering in those two major categories.

Second, we can talk about in each of these categories two subcategories. These too have been alluded to. One of these would be what we call gene therapy, where we correct a defect that is there, and a second one which, for want of a better term, I would call gene cosmetic surgery, because we would be improving, or not necessarily improving but at least altering a certain characteristic or trait.

The possibilities, both technically and otherwise, for these different technologies, in the two major categories, with the two subtypes of uses, are dramatically different. And that is what I would like to briefly go over today.

I think it is important for us to recognize that we are talking about a technology, genetic engineering technology, which really consists of a series of techniques. And this series of techniques includes, but are not comprised solely of, the actual genetic manipulation itself. This is very important to bear in mind because, to make a technology successful, or to make it useful in a clinical setting or in a regular societal setting, the entire technology has to make sense. And that is what the example I will go through will highlight.

As a preface to that example, let me mention that in other types of technologies, in the production of a certain substance, we always have alternative ways to reach whatever end goal we might have in mind.

In the production of insulin, for example, we could very easily do what the chemists do and take chemicals off a shelf and just link them up and produce insulin by chemical means. This was achieved 30 years ago for the first time, and in the 30 years that have elapsed I don't think any company or any group has really used this method to produce insulin.

Economic factors and other factors are very important considerations when you consider whether a technology will actually be used.

There are alternatives of course, such as the extraction of insulin from pancreatic tissue, the standard method, and now of course as of the last few weeks we have recombinant DNA through fermentation as a production method of insulin. So there are several ways to achieve a certain end.

Now, getting back to genetic engineering as a technology, I will walk through the first kind of genetic engineering which would be a prenatal genetic engineering, and this would be, as the name implies, before birth and most likely would be at a very early stage. It would be at either the fertilized egg stage or at least when there have only been a couple of divisions so you don't have too many cells that have to get the appropriate genetic material.

There are several steps involved and, as we go through each of these steps, let's see whether the technology makes sense.

First of all, an average parent, average parents are parents or parents-to-be, would not walk into a physician's office and simply say, test me for all the hundreds of possible genetic diseases and make sure my offspring won't have these. As a practical situation, there has to be some reason why these parents would go into the clinic. And in general terms either there is a family history, or when diagnostic tests are available the parents might be tested for certain types of suspected disorders. As a result the parents might suspect that their offspring might be the carrier of a particular gene.

So first we have to have diagnostic tests available before anybody would even consider doing genetic engineering on a large scale.

These genetic tests for the carrier status are now being developed. We only have a handful of them, only a dozen or so. But the tests are being developed with the new recombinant DNA techniques for such diseases as thalassemia, sickle cell anemia, growth hormone deficiency, deficiency of an enzyme that leads to Lesch-Nyhan Syndrome and certain other diseases. Others are being developed for such disorders as Huntington's chorea or certain hemophilias. But these are under development now. They do not exist today.

But let's assume we get past this stage in the technology and we have some diagnostic method to determine which parents might request this test for the children.

Then you would have to go to the next stage and determine which fertilized egg, or if there is one fertilized egg, if that egg has the defect. Otherwise, why go through an elaborate procedure, a surgical, genetic surgical procedure if that particular fertilized egg does not have the so-called abnormal gene or genes.

Well, today we are really faced mostly with genetic diseases which are recessive, which as you know means that the parents would both have to be carriers to give an offspring that would have the disease itself—not all of course, but generally this is what we are talking about.

This means, then, that if you follow Mendel's laws of inheritance that on the average out of every fertilized egg you will have that one abnormal egg, and three normal ones. So already, as you view the overall technology, at least to me it does not make sense to carry out an elaborate surgical procedure on that one fertilized egg, try to alter that, when there are three others that might be normal. Simply take the normal ones and put those back into the womb to allow further development.

This does raise ethical questions about what you do with that one fertilized egg which was abnormal. But I would suspect it is the lesser of two evils to simply discard that one, allow one of the three normal ones to grow, than to simply go through this elaborate surgical procedure on that one egg.

To carry this one step further, we have to have a diagnostic step—I am sorry—first you have to have genetic engineering itself.

Mr. GORE. Let me say that a lot of people would violently disagree of course with——

Dr. HARSANYI. The second step.

Mr. **Gore** [continuing]. With the conclusion you reached just before moving on. But go ahead.

Dr. **Harsanyi**. Yes; I agree. I fully realize that many people would. But putting it into that framework, as to what are the possibilities, what are our choices, if it comes down to one or the other, I would think it would be more reasonable, I think even to those who are opposed to abortion, to have that single egg, single fertilized egg, the normal one, develop rather than the abnormal one develop. When you are sitting there in the laboratory making a choice between one or the other, I think they would argue, even those opposed to abortion, that it would be more logical to let the normal one develop.

Then the third step is the actual genetic engineering. To my knowledge, this has not been carried out in human beings. We have heard some of the problems we would face in actually trying to get a gene, a particular gene into the egg, then have it go to the right spot on the right chromosome, and have it be expressed properly throughout development.

The fourth step would be to determine whether the change actually occurred, once you introduced the gene into the egg. And this is very important.

What Dr. Sanford mentioned with regard to the mice, if you recall, referred to a population, a set of experimental animals. It was not one mouse with one egg that was manipulated. In some cases the gene is incorporated, in some cases it is not. So when we are faced with a real human life situation, we are talking about one individual. And we have to make sure that, if we want this to be an effective surgical procedure, that in fact that particular gene gets incorporated.

Finally, you have to carry out the surgical procedure for reimplantation. This is one area of course where medicine has moved fairly rapidly, and this brings up the whole question of in vitro fertilization. But as a technology I think we are fairly well along there. So I won't use that as a limiting step now.

All of these steps that I have mentioned must be achievable in the overall technology before it makes sense to continue.

Let me mention one other example, then, actually two other examples. One other example of the prenatal surgery, and this is the prenatal genetic engineering for traits which I had called earlier cosmetic surgery rather than therapy and these are the ones you have referred to as possibly whimsical, and in fact I agree, these are probably ones that people would describe as arbitrary and possibly even elitist.

These traits that we are talking about are not ones that you can choose from the parental complement. Usually what we are talking about are two parents who say, we may both be short but we would like to have a tall child, let's introduce a gene from some exogenous source.

So the arguments I have mentioned so far are not valid for that. You have to introduce something. It is not just choosing from the normal fertilized eggs from the original parents.

I submit that in such a case we are almost always, and this reiterates something that has already been said, we are always going to be dealing with very complicated genetic traits, multigenetic traits. And if it is difficult enough, as Dr. Axel has mentioned, to introduce that one gene the correct way; to introduce 5, 6 or 10 genes, all of which are expected to work in concert, I would say that perhaps some day this might be achieved, but we are nowhere near to achieving that.

Whatever trait I could ask anybody to point out which might be desirable, intelligence—well, psychologists cannot even agree what the term means, much less talk about finding genes for it; body size, almost every animal has a dozen genes or more for body size; strength, speed, agility, whatever we can think of really consists of a number of genes working in concert through the development, genes that affect muscles, the nervous tissues, and so forth and so on, all of them working in concert.

Mr. GORE. Let me ask you at that point, have scientists not developed with the genetic engineering techniques a synthetic or some kind of hormone that can be used to artificially accelerate growth, and in the terms of your example allow those hypothetical parents to have a child much taller than either the mother or the father or any of the grandparents?

Dr. HARSANYI. In those situations—there are two types of increases in growth. There is the type in which all the tissues and all the organs of the body grow uniformly, proportionately, and there is a type of growth which would occur if we used these hormones excessively in which we would have the acromegalic type of syndrome; in other words, an individual with lengthened bone structure and disproportionate-sized hands and so forth.

To answer the question, I don't think we are at a stage where we can give a single substance and dramatically increase the overall size of an individual from let's say somebody who is a short individual to somebody who would be a football player, but proportionately so.

To conclude, I will focus on only one of the two remaining types of genetic engineering, both of which are in the postnatal area. There, too, you can have the postnatal cosmetic surgery, but that is a trivial one, because it is a category I cannot really imagine too many uses for that technology; maybe change in hair color, but I really cannot think of too many uses for that.

Postnatal gene therapy, however, is what we have been referring to; Dr. Axel certainly talked about that. And I think this is the one type of genetic engineering where eventually and very shortly we will probably see some possible attempts. It has already been attempted, as you know, and I think this is one area where we might expect, not only technical but technlogical success. I think both of those characteristics have to be included.

I would say that with sufficient care we can proceed ethically, and I believe this postnatal gene therapy, this one last category, will in fact be a reality in the near future.

Thank you.

Mr. GORE. Which was that?

Dr. HARSANYI. The postnatal gene therapy, such as the cure of a single organ within somebody who has already been born, a child or adult.

[The prepared statement of Dr. Harsanyi follows:]

HUMAN GENETIC ENGINEERING TECHNOLOGY: HOW LIKELY?

The techniques of gene transfer which have been described today have been carried out in lower organisms -- in bacteria, plants, and lower mammals -- not in man. But as we learned during the Office of Technology Assessment's study on the Impacts of Genetics, the fear that many people hold is what the bioethicists call "the slippery slope". This is the conviction that whatever is achieved in lower organisms today will inevitably be done in man sooner or later. I would like to address the question of where we are in genetic engineering technology by examining the different ways in which the technology might be applied and then examining the components which make up the technology. I submit that the kinds of genetic engineering which are likely to be used successfully are not very different from other surgical procedures. On the other hand, the kinds of genetic engineering which tend to frighten people are not likely to be used for a variety of reasons, only one of which is technical.

Genetic engineering is not merely the act of transferring a segment of DNA from one cell into another. As a technology for altering genetic material of human beings, genetic engineering actually consists of a series of techniques. And each of these must prove to be not only technically feasible but must be competitive with other, alternative operations to achieve the same desired end.

What are these desired ends? Where are the technologies to be used? They can be divided into two major categories, each of which, in turn, has two rather different applications. These categories are postnatal genetic engineering, which is carried out on a child or adult, and prenatal genetic engineering, which is performed very early in embryonic development. The distinctions are important because the level of the technology, the consequences of their use, and the issues they raise are very different.

Postnatal Genetic Engineering

As the members of the Committee know, practically every cell in every tissue of the human body has a full set of genetic material, the chromosomes. The reason that liver cells are liver cells, however, is because a specific set of genes is active, i.e., perform their particular functions in those cells, whereas in kidney cells, a different set of genes is active. As an example, the cells which eventually mature into erythrocytes, or red blood cells, have genes which are active for hemoglobin production. The beta cells of the pancreas, on the other hand, have essentially the same genes, but in those cells these genes are inactive. The point of all this is that if we wish to replace a defective gene for globin, the gene doesn't have to be replaced in every single cell of the body -- only in those cells where the genes are active. If we wish to replace the gene which determines sickle cell globin, only the cells of the bone marrow need to be altered. Hence one major category of genetic engineering is the alteration of genetic material only within a single tissue, such as the bone marrow. This procedure would be carried out on the fully formed child or adult. Because this procedure is in essence very similar to the transplantation of an entire organ from one individual to another, it might be termed "gene transplantation". The tissue of a patient would be removed, the genes would be transplanted, and the same tissue would be returned to the patient.

There are, however, two types of applications of this category of genetic engineering. First, there is the replacement of so-called defective genes with normal ones. This is referred to as gene therapy. But there is also the possibility of altering one genetic type for a different, more desireable type. This is not strictly therapy, in that there is no pathology involved. For want of a better term, it might be appropriate to call this type of genetic engineering, gene cosmetic surgery. I suspect that it is this application, expected to be arbitrary and elitist, which troubles most people, and which at once brings back dark images of actual past eugenics programs and the future possible programs of Aldous Huxley's Brave New World.

Prenatal Genetic Engineering

The second category is the alteration or replacement of the target gene or genes in every cell of every tissue. Technically, the operation would have to be performed on the single cell (egg or sperm), the fertilized egg, or very early on the developing embryo when there aren't too many cells which need to be altered. As in the case of gene transplantation, there are two types of applications: gene therapy and gene cosmetic surgery. This category of genetic engineering would have to be employed either when many different organs require the active healthy genes or when the desired gene must function during the development process itself. Once again, I suspect that gene therapy, which aims to prevent pain and suffering, is not viewed as negatively by the public as gene cosmetic surgery.

Component Procedures in Genetic Engineering

Each of the four types of genetic engineering -- prenatal gene therapy, prenatal gene cosmetic surgery, postnatal gene therapy, and postnatal gene cosmetic surgery -- must be examined separately, not only because the consequences of their use are different, but also because the component procedures used in the overall technology are at different stages of development. What are these procedures or steps?

Take the example of two parents who might desire to alter the genetic endowment of their child-to-be. If it is a case of potential gene therapy, the following steps would have to be taken:

1. Determine whether the parents carry a defective gene, i.e., will their offspring need to be a candidate for gene manipulation?

Clearly, only those parents who have reason to suspect that their child will be born with a particular defect would consider gene therapy to correct that defect. It follows that some method must be available for identifying which parents might pass on a defective gene. For most genetic diseases, the only indication that a parent might carry a particular defective gene is the family history. However, it is still very difficult to establish whether any one individual actually does carry the defective gene. With the advent of rDNA techniques, some progress has been achieved. The DNA of a single defective gene can be used as a diagnostic probe to determine if an individual is heterozygous (a carrier) for a recessive gene. This is now possible for the single gene defects thalassemia, sickle cell anemia, growth hormone deficiency, hypoxanthine phosphoribosyl transferase deficiency (Lesch-Nyhan syndrome), and certain collagen diseases. Genes defective in a variety of cell products, such as blood clotting factors (hemophilias), are being sought. But even in those cases where the product of the gene is unknown, such as in Huntington's chorea, gene probes can be expected to detect the presence of an abnormal gene. These do not yet exist.

2. Determine which cell is to be the target for genetic engineering.

Even if the would-be parents are identified as being at risk for producing a child with a genetic disease, it must be established that the fertilized egg or embryo carries the abnormal gene. Otherwise, why operate? By far, most serious genetic disorders, for which prenatal detection might be sought, are recessive. This means that both parents are carriers; which, in turn, means that on the average one out of four fertilized eggs will carry two copies of the abnormal gene necessary for the trait to manifest itself. It is this fertilized egg, or the embryo evolving from this egg, which would be the target for engineering.

Two points are worth noting. First, diagnostic techniques such as gene probes are not sufficiently sensitive to determine whether a single cell or even a few cells carry a particular gene. Nor would the cell remain unharmed! Today, an embryo must be between 16 and 20 weeks old before the gene can be detected. If, as it is likely, we will soon be able to detect the gene as early as 8 weeks after conception, there are already thousands of cells in the embryo. Secondly, even if our techniques become so refined that we will be able to detect early enough that one abnormal embryo out of four, it will make no technical, medical, or economic sense to alter it genetically. Certainly if we can identify the one embryo with the abnormal gene, we will be able to identify the three embryos with normal genes. Couple this with the fact that detection at this early stage will be done most likely in vitro, it is also likely that several fertilized ova will be available for examination. Avoiding the ethical arguments at this time, I contend that it will be far more medically sound to select one of the three normal embryos for reimplantation than to try to alter the one abnormal embryo genetically. In short, in view of the alternative, genetic engineering simply doesn't make sense as a practical procedure to obtain a normal embryo.

3. Carry out the actual genetic engineering itself.

The actual engineering, to my knowledge, has never been carried out on a fertilzed human ovum or early embryo. Mammalian studies indicate that genes can be introduced into a fertilized egg, but even the procedures described to date cannot guarantee that any one egg will take up a particular gene and incorporate it stably into its own genetic complement. Nor has the gene been shown to be active when and where its natural counterpart would be. Nevertheless, I believe that these obstacles will eventually be overcome.

4. Determine whether the change actually occurred, i.e., was the engineering successful?

Once the gene transfer has been attempted, some diagnostic method would be needed to establish the success of the procedure. The method may or may not be similar to Step #2, but would most likely have to be noninvasive. To date, none exists. In the absence of such a test, it would be an unacceptable gamble whether the embryo would develop into a normal neonate.

5. Carry out the surgical procedures for reimplantation.

It should be clear that the genetic manipulations, including the detection steps, would not be carried out within the womb. Since the early embryo would be treated _in vitro_, the technique of reimplantation would have to be sufficiently developed. To date, despite much progress, the success rate of _in vitro_ fertilization has been low but improving. It is difficult enough to reimplant a normal fertilized egg, much less one which had been genetically manipulated and tested.

All of these steps in the overall technology must not only be technically feasible, but must have a rational, compelling reason for use. I find it difficult to believe that all these manipulations would be preferable socially, ethically, economically, or otherwise to the simple alternative of selecting one of the normal fertilized eggs.

The example of prenatal gene cosmetic surgery raises similar doubts of practicality at this time or even in the forseeable future. In this case, however, the argument cannot rest on whether its easier to select one of the normal eggs because apparently all are "normal". Here, some other genetic trait, not present in either parent, must be obtained from elsewhere for transfer.

The problems of detection and the genetic transfer itself not only remain, but are compounded severalfold. All the candidates for gene therapy have been single gene traits. The candidates for gene cosmetic surgery will be far more difficult to handle -- or even identify. Assuming that the would-be parents decide which traits they desire, it will be a major task to select which genes need to be transferred. What might some of these traits be? Intelligence? Psychologists can't even agree on how to define it, much less find the genes that promote or influence it. Even if we break the definition of intelligence into such components as "mathematical reasoning", "verbal skill", "good long term memory", etc., it is safe to assume that many genes will be necessary for recognizable improvements. Body size? In every animal, more than a dozen genes are involved, spread over several chromosomes. This means that several genes would have to be found, transferred, and placed in the appropriate chromosomal position for proper functioning. Strength? Speed? Agility? Oratory skills? There's no single gene for those -- the traits are the sum total of a variety of genes which act synergistically to affect the structure and function of muscle, nerve, and other tissues.

The example of postnatal gene cosmetic surgery is a likely near term possibility, but it is a trivial one. Most organs have an established shape and structure which limits the properties which a new gene could confer upon it. One of the few non-therapeutic changes one might imagine as desireable would be in hair pigmentation. Even there the alternatives are obviously simpler; hence genetic engineering as a technology to bring about alterations does not loom on the horizon.

But the example of postnatal gene therapy is likely in the near future, not only because the technique will be developed for it but because there are several important genetic diseases of abnormal blood which can be traced to single genes. A disease such as thalassemia claims the lives of 200,000 children annually, according to the World Health Organization (reported in Nature 298: 416, 1982), and the prevalence of the defect in the United States has recently been shown to be higher than originally thought (Arch. Intern. Med. 142: 1280, 1982). Alternative methods of treatment are only palliative, and children don't ususally live more than 20 years with current blood transfusion treatments. Only recently has bone marrow grafting for the disease been reported to be successful for two patients (Med. World News, Sept. 13, 1982, p.53), although it remains a risky operation.

In summary, the technique of transferring genes into cells of living human beings will likely be accomplished. When and where the technique will be used -- pre- or postnatally, for therapy or cosmetics --will vary considerably. Even if all the technical difficulties can be overcome for each component of the overall technology, it is hard to see how the technology could replace the available alternatives. With sufficient care that we proceed ethically, however, I believe that postnatal gene therapy will be a reality in the near future.

Mr. GORE. Thank you very much. Dr. Jackson, you expressed such skepticism about the possibility that human genetic engineering will ever be possible. How do you react to this last statement by Dr. Harsanyi, that in that case at least it will be possible very quickly? And other witnesses are going to tell us that basic human gene therapy may begin within 5 to 10 years. In fact, some witnesses on the next panel will so testify.

Mr. JACKSON. Well, let me try to reiterate what it was I said, which may not have been adequately clear.

I did say that for a certain class of genetic diseases, principally those of organs such as the blood or, as Dr. Axel has mentioned, the bone marrow, which can be accessed easily, can be manipulated in the laboratory, and can be reintroduced into individuals, there I believe, and I so stated in my testimony, that within the next several decades it will be possible to do genetic engineering, and quite possibly successful genetic engineering in those areas.

I don't think we should minimize the problems that are involved. And I think that Drs. Axel and Sanford and Harsanyi have all gone into them in more detail than I did in my general statement.

The point at which I am pessimistic about gene therapy is in precisely the area that Dr. Harsanyi has just also said that he is pessimistic, and that is in terms of complex multigene traits. I emphasized that point to the extent that I did because I think that much of the popular misunderstanding about genetic engineering and the capabilities of it is precisely focused around such traits as intelligence or personality, or what you have referred to as the whimsical kinds of things that might be done with this technology. These are the types of human genetic engineering that many people are thinking about and that much of the writing in the popular press is concerned with.

I think it is very important that we recognize the technical difficulties associated with doing successful genetic engineering for such multigene traits where, for most of them there is still disagreement as to what extent the determinants of these traits are genetic, and to what extent they are environmental. Even to the extent that everyone agrees some of the determinants are genetic, we have no clue as to what those determinants are at the level of their biochemical mechanisms.

We are just so far at precent from being able to deal in any kind of knowledgeable and directed way in affecting such traits that I believe to pretend otherwise is to mislead the public about a very important issue.

Mr. GORE. Well, as I said earlier, there is disagreement, and disagreement on the part of responsible scientists, some of whom will testify on the next panel, which will be the last panel of the day.

Dr. Axel, you spoke of the problems that could result should a newly inserted gene disrupt or even kill the host cell.

And Dr. Sanford, you also discussed these hazards.

Let me ask the two of you, what sort of experiments will be necessary to insure that this does not occur? In other words, how will we know when and whether a particular treatment, genetic therapy, will be safe for human beings.

Dr. AXEL. One can anticipate an idealized form of gene therapy in which the newly inserted gene ultimately inserts itself in place of the mutant gene. Now, if you consider that potential, then the probability of harm is minimized, because all you have done is in theory replaced the mutant gene with a wild type or normal gene. That technology in animal cells, higher organisms, has not yet been developed.

On the other hand, that technology in lower organisms has been developed. And so I think that is one important area of investigation. And if solved in the way I just suggested, it would I think dramatically limit potential for harm.

Now, then you might ask, well, suppose that all other problems are solved and we are left with this one—where do we go with respect to gene therapy?

We can obtain the accumulated experience of animal model systems and ask just how frequently does gene insertion harm the recipient cell in animal model systems. And one can make a risk estimate on the basis of extrapolation to those systems, remembering that the sorts of cells you wish to insert genes into are sick to begin with, and in many instances they are nonfunctional. So the death of a specific subpopulation of cells which is not functioning anyway may not be a serious consequence.

Mr. GORE. Dr. Sanford, do you want to comment?

Dr. SANFORD. The experiments that I was talking about were not really undertaken as gene therapy, but as an attempt to find out more about the processes that are involved. What goes on when you insert a gene into a cell, what difference it makes where it is located and so forth. I think that is the area where we need to concentrate our attention in relation to gene position for example, there are experiments in lower organisms that suggest that it should be possible to direct a human gene to a specific correct site on a chromosome.

We still need to know more about how transferred genes are expressed. We know that in normal development all genes are not expressed all the time. We know very little about how this expression is controlled. People have wondered, for example, whether methylation of an inserted gene may have some effect on whether or not the gene is expresed, especially since methylation seems to play a role in gene activation in normal development.

If we could understand the processes involved in gene expression, we would be a long way closer to knowing what the next step should be technically in developing methods for effective gene transfer.

Mr. GORE. Will any human experiments be necessary to answer those questions?

Dr. SANFORD. Ultimately, if you are going to work with gene therapy, you will have to look at the risk-benefit ratio and where this is considered favorable, proceed with working in human patients. prior to this stage, there are many animal models that can be used, where you can use genetically identical animals, and look at the effect of manipulating a specific gene. We have much more to learn in animal models before we should be concerned with attempts at studying gene transfer in patients.

Mr. GORE. Now, on the third day of these hearings, Thursday, morning, we are going to hear from Dr. Martin Cline. What in your opinion, and I would like to ask other members of the panel the same question—what in your opinion was scientifically premature about Dr. Cline's experiments?

Dr. SANFORD. I think the general comment that I just made still pertains. It would be much more desirable to have a better understanding of how the gene will function if you succeed in inserting it into the cell before you proceed with the experiment in patients.

Mr. GORE. Dr. Axel?

Dr. AXEL. I agree with you. The Cline experiment was scientifically premature. I posed a number of problems and I also posed potential solutions before gene therapy could be anticipated. Those problems included the efficiency of gene transfer, disability, and appropriate levels of gene activity. At present, and at the time Dr. Cline attempted these therapies, these problems had not been solved. In fact, they are not completely solved at present.

As I pointed out, those are three of several additional problems that need to be solved, which will be solved before I think we can anticipate gene therapy.

Mr. GORE. Dr. Jackson?

Dr. JACKSON. I would agree with both Dr. Sanford and Dr. Axel. If you look at the data that was published by Dr. Cline himself, as well as the rest of the field, it was clear that there was very low probability for success, based on his own data, using that particular technique.

Mr. GORE. Dr. Harsanyi?

Dr. HARSANYI. I think you have unanimity here. Just as a simple example, we don't know when we introduce a gene into a cell where that gene will finally find a home, on which chromosome and so forth. And if it finds a home somewhere where it might disrupt cell function, we obviously have a problem. We cannot direct it yet. We are not at that stage yet. So it is still a question of chance.

Mr. **Gore**. Dr. Axel, in our next panel we will explore the concept of gene mapping on humans in more detail.

Could you generally explain what gene mapping is, and what is involved in it?

Dr. **Axel**. Well, if indeed your next panel is to describe this in detail, let me just briefly say that gene mapping at a molecular level would define the relative position of genes on chromosomes—where the gene is and who its neighbor genes are.

The potential significance of this mapping at a molecular level, since genes are the ultimate harborers of mutations, would be to identify mutations, either by changes in the genes themselves, or by the association of other changes in neighboring genes.

Mr. **Gore**. Now, the technology of gene mapping uses what—computers—to store the information? What to gather it?

Dr. **Axel**. The technology of gene mapping initially utilizes techniques of—can utilize techniques of recombinant DNA to isolate genes; ultimately, by using a procedure known as molecular hypridization, identify on which chromosome a gene resides, where on that chromosome this gene resides and then, by additional studies utilizing rather simple technologies, one can identify who the gene's neighbors are, what other genes are in the vicinity.

The wealth of information that will emerge, considering that the human gene has the potential to accommodate 10 million genes, requires that this information be sorted ultimately through computers.

Mr. **Gore**. Dr. Sanford, you conducted experiments at your laboratory in which human blood genes were injected into mice embryos, correct?

Dr. **Sanford**. Correct.

Mr. **Gore**. One mouse actually retained the human gene after birth; is that correct?

Dr. **Sanford**. That is correct.

Mr. **Gore**. But that mouse did not pass the human gene on to its offspring?

Dr. **Sanford**. Also correct.

Mr. **Gore**. Do you know why?

Dr. **Sanford**. No; I think that that is another example of genetic processes that we need to investigate.

Mr. **Gore**. Do you see any point at which the line should be drawn where the insertion of human genes into other species is concerned?

Dr. **Sanford**. If you take a gene that happens to have been cloned in a human, but is made up of a series of chemical bases very similar to the gene for the same trait in a mouse, and use that in an experiment, it seems an overreaction to say that that is dangerous or is crossing a barrier. On the other hand, I agree with the point made earlier by Dr. Capron that there is a continuum in terms of concern about the degree of genetic alteration.

Mr. **Gore**. It would certainly seem like an overreaction to me, too. But at some point a line will have to be drawn. And I am just wondering what you would look for in your experiments say in the next 20 years as your techniques got more sophisticated. It is an unfair question because no one has really confronted it.

Dr. **Sanford**. I think that probably while we are dealing with, single mutant genes, we are less likely to run into this question. It will be when we get into more complex traits—such as intelligence—that we will face this type of question.

I think it is true that we cannot just pass this problem off by saying that it is so far away that we don't need to worry about it. I agree with you we do need to worry about future possibilities, and that the time to start thinking about these questions is now. I don't have a specific suggestion about determining how such a line should be drawn.

Mr. **Gore**. Well, in summation, it seems to me that what the four of you are saying on this panel is that the development of this technology will probably limit the number of scenarios that are conjured up when one addresses the bioethical concerns with human genetic engineering. And we will be dealing eventually with a subset of those concerns due to the pattern of the evolution of this science.

Is that a fair summation of what you are saying?—among other things, I know.

Dr. **Harsanyi**. I would say from my point of view that was a perfect summary of at least what I feel.

Dr. **Sanford**. I think we are trying to convey to you the enthusiasm we have about these approaches, but also sharing with you the concern that there must be thought about the future. For the applications likely to be possible in the immediate future, certainly we are very enthusiastic.

Mr. **Gore**. Dr. Axel?

Dr. **Axel**. I agree. I think it is important to additionally point out that the sorts of frightening scenarios that we frequently encounter are scenarios that derive largely from wild imagination fears, and frequently fantasy. But we have to weigh those thoughts, if they may be called thoughts, against real potential benefits. So we can talk of real potential benefits in the future, countered with vague notions which derive frequently from fantasy. And those are not equivalent arguments.

Mr. **Gore**. Dr. Jackson?

Dr. **Jackson**. The technology will, as you have stated in what I think is quite a good summary, limit very much the kinds of options that we have to worry about in a concrete sense in the near future.

I want to come back to something that you said in your opening statement, and Dr. Capron and the commission also emphasized, and that is that education is of prime importance in terms of having the discussion held in the kind of open fashion that I think this whole area has been treated in now for the last 10 years, and allaying many of the kinds of fears and fantasies that we are concerned about, because they are based not on scientific reality in many cases but on projections which are themselves a type of misunderstanding.

Mr. **Gore**. Well, let me say again something that I said in discussion with Dr. Capron.

I do believe that there is a danger of overreaction on the other side, and I speak as a representative of 500,000 people in middle Tennessee, many of whom are troubled by the course of development of this science.

It may be that there is an overreaction to some of the stories or scenarios that come out of discussion of human genetic engineering but, by the same token, I think there is a danger of misunderstanding on the part of scientists and an overreaction to the public's apprehension, and a tendency for scientists to say, "They just don't understand, they just have a misguided view of this." Because I think there is a great deal of genuine on-target concern that the public has a better grip on than the scientific community a lot of times.

What I am saying is that the scientific community, where this subject is involved, cannot say just more understanding will dissipate these concerns, because we are dealing with the consequences of success, as I said earlier, and the questions that are raised are so profound that I really believe very deeply that we have to develop an unprecedented debate that involves the general public and the scientific community about all of the implications of this new technology. I think it is a landmark in the history of mankind, the development of this technology.

You wanted to say something?

Dr. **Sanford**. I was just going to add something.

I am sure, that you know, that the people who first raised this concern as a public issue were geneticists. Geneticists are perhaps a special breed among scientists. I think you go into the study of genetics partly because you are interested in what life's characteristics are inherited, and what will happen not only to our own generation but to all the generations of the future.

I think and I hope that you will find that the geneticists will be among the most responsible members of the public that will be involved in this debate.

Mr. **Gore**. Well, I certainly hope so. Certainly the testimony that you four have given would lead one to be optimistic in that direction.

I want to thank you for the excellent contributions you have made here today. Thank you all.

Mr. **Gore**. I would like to call our final panel now, Dr. Yuet Wai Kan, Dr. Mark Skolnick, Dr. Theodore Friedmann, and Dr. Anderson.

Let me say I am going to call for a 5-minute recess before we start this panel. We will be back in 5 minutes.

[Recess.]

Mr. **Gore**. The subcommittee will come back to order.

I would like to call our final panel of today.

Dr. Yuet Wai Kan, professor of molecular hematology, University of California School of Medicine, San Francisco, Calif.; Dr. Mark Skolnick, associate professor of human genetics, University of Utah College of Medicine, Salt Lake City, Utah; Dr. Theodore Friedmann, professor of pediatrics, University of California School of Medicine (San Diego), La Jolla, Calif.; and Dr. French Anderson, Chief, Laboratory of Molecular Hematology, National Institutes of Health, Bethesda, Md.

Gentlemen, I would like to welcome you to the subcommittee.

Dr. Skolnick will be joining us momentarily.

Dr. Kan, without objection, the text of your statement will be put into the record at this point. I will invite you at this time to proceed with your testimony.

STATEMENTS OF DR. YUET WAI KAN, PROFESSOR OF MEDICINE, UNIVERSITY OF CALIFORNIA SCHOOL OF MEDICINE, SAN FRANCISCO, CALIF.; DR. MARK SKOLNICK, PROFESSOR OF MEDICAL GENETICS, UNIVERSITY OF UTAH COLLEGE OF MEDICINE, SALT LAKE CITY, UTAH; DR. THEODORE FRIEDMANN, PROFESSOR OF PEDIATRICS, UNIVERSITY OF CALIFORNIA SCHOOL OF MEDICINE (SAN DIEGO), LA JOLLA, CALIF.; AND DR. FRENCH ANDERSON, CHIEF, LABORATORY OF MOLECULAR HEMATOLOGY, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MD.

Dr. KAN. Thank you, Mr. Chairman.

In this presentation, I will discuss the application of recombinant DNA technology to the diagnosis of genetic disorders, specifically the hemoglobin disorders.

The first clinical application of recombinant DNA technology has been in the hereditary disorders of hemoglobin synthesis. It has already provided a safe and reliable method for prenatal diagnosis of sickle cell anemia and thalassemia, and similar approaches are being developed for many other genetic disorders.

Sickle cell anemia occurs primarily in people of African origin, but is also seen in Mediterranean populations and in Asians. In this country it is estimated that about 50,000 black Americans have sickle cell anemia.

Affected individuals have lifelong hemolytic anemia and recurrent painful crises. Common causes of infant mortality include infection, severe anemia, and thrombosis of blood vessels of the central nervous system. In older patients, cardiac and renal failure are frequent causes of death.

The clinical manifestations of sickle cell anemia are extremely variable; some patients experience recurrent debilitating episodes of the illness, while others have milder manifestations. At present it is not possible to predict the severity of the disease in a given individual.

The common feature of thalassemia is inadequate production of one of the two components of normal adult hemoglobin—alpha and beta globin. The most common thalassemia syndromes are alpha and beta thalassemia in which synthesis of either the alpha or beta globin chains is impaired respectively. Although alpha thalassemia occurs in many countries, the severe homozygous form of the disease occurs predominantly in Southeast Asia. In the United States this condition is primarily seen in people of Asian descent. An affected fetus dies in utero during the second half of pregnancy, or immediately after birth.

Beta thalassemia, or Cooley's anemia, is prevalent throughout the world and constitutes a major health problem in people from the Mediterranean area, the Middle East, and Southeast Asia. In this country, it primarily affects people of Italian and Greek origin.

Until recently, patients affected by homozygous beta thalassemia usually died at a young age from anemia or infection, although some lived into their twenties and succumbed to a cardiac failure. New methods of treatment have now increased the life expectancy and enhanced the quality of life for many of these patients. The treatment program prevents the organ damage from the anemia and iron overload and enables many patients to experience normal physical development. Nonetheless, the transfusions, daily injections, and recurrent hospitalizations necessitated by the program impose a great emotional and financial burden on the patient and his/her family.

Dr. KAN. Sickle-cell anemia and thalassemia are inherited according to Mendelian laws. If both parents are carriers of these diseases (each one has one abnormal gene), then there is a 1-in-4 chance that their offspring will inherit both abnormal genes and suffer from the homozygous disease. Carriers themselves are asymptomatic, but can be detected by a blood test.

An alternative available to parents at risk for bearing children with genetic disorders is prenatal diagnosis. This option has been used for many years to diagnose such diseases as Down's syndrome, Tay Sachs disease, and spina bifida in the unborn fetus. The first prenatal tests for sickle cell anemia and thalassemia were developed in 1974.

At that time, the disorders were detected by studying fetal blood which was obtained by fetoscopy or placental aspiration. The placenta is first localized with ultrasound and a fiberoptic instrument (fetoscope) is inserted into the uterus to permit direct visualization of a blood vessel on the placenta or in the umbilical cord.

A blood sample is aspirated with a small-gage needle contained in the instrument and analyzed for the type or quantity of hemoglobin synthesized by the fetus.

The fetal blood sampling procedure has several important disadvantages. It requires highly specialized training, and few obstetricians perform the procedure.

In the United States the procedure is routinely available in only two medical centers, New Haven and San Francisco, which means that patients must travel to these centers, often at great expense or over long distances, to undergo the test. More importantly, fetal blood sampling carries with it a risk of fetal mortality of up to 5 percent.

A safer and more established technique for prenatal diagnosis is amniocentesis. First introduced as a method of diagnosing hereditary disorders in the fetus in the late 1960's, amniocentesis is now used to prenatally detect over 70 genetic abnormalities. It is available in many medical centers throughout the world.

At approximately the 15th week of gestation, a sample of amniotic fluid is taken from the amniotic cavity and, depending on the disease in question, either the amniotic fluid or the cells (which are both fetal in origin) is analyzed. This procedure is known to be safe.

Through recombinant DNA technology, sickle-cell anemia and thalassemia can now be diagnosed in the fetus using amniocentesis.

The first step in the chain of events that lead to the application of DNA analysis techniques to prenatal diagnosis was the discovery of restriction endonucleases in the early 1970's. These are enzymes that cleave (cut) DNA at a particular nucleotide sequence. Over 100 restriction enzymes have been characterized, each cleaving the DNA at a specific sequence.

Then, in 1975 Edward Southern devised a technique for analyzing the genome of higher organisms using restriction enzymes.

Finally, in the late 1970's, the human globin genes were isolated, and the Southern technique was used to study the human hemoglobin diseases.

I have a couple of slides to show.

This slide illustrates the southern technique.

[Slide.]

Human DNA is first digested with a restriction enzyme—this upper left corner illustrates DNA and the blue arrow shows the cleaving of the DNA with one of these enzymes—this generates anywhere from a few hundred thousand to several million DNA fragments of different lengths. These fragments are separated according to size by electrophoresis on a gel support medium and are then transferred to and immobilized on special filters.

A radioactive probe specific for the globin gene under investigation is synthesized in vitro and used as a hybridization probe for the DNA fragments.

Only the fragments that contain globin genes will hybridize with the probe. The filters are exposed to X-ray film, and the globin gene-containing fragments are visualized.

Mutations in the DNA in sickle-cell anemia and thalassemia can thus be identified directly. Furthermore since any nucleated cell contains all the genetic information required for the analysis, amniotic fluid cells can be used as the source of fetal DNA.

[Slide.]

This illustrates the approach now used to diagnose sickle-cell anemia. A restriction enzyme called Mst II cleaves normal DNA at the position corresponding to amino acids number 5, 6, and 7 of the beta globin chain. This is shown on the left-hand side.

The sickle mutation affects the nucleotide sequences at the beta 6 position and abolishes the Mst II recognition site. The enzyme no longer cleaves the DNA at this sequence and hence a long DNA fragment is produced instead of the short ones normally seen. These differences in fragment length enable us to distinguish a normal fetus from one affected by sickle-cell anemia.

What we use here is a radioactive probe which has been isolated from the human gene using recombinant DNA technology to probe the DNA digested with enzyme Mst II.

The normal DNA will produce a 1.15 kilobase fragment, whereas the sickle DNA will produce a longer piece of DNA. So one can read off the gene-types of the individuals shown on the slide. The first two lanes are from people who are heterozygous or carriers of the sickle gene. The third lane in the X-ray film is from a normal individual and the fourth is from one affected by sickle-cell anemia.

The DNA analysis technique can also be applied to alpha thalassemia. Since the lethal homozygous form of this disorder is caused by deletion of all the alpha globin genes, it can be diagnosed by demonstrating the absence of the alpha globin genes in the DNA.

[Slide.]

This shows results from another DNA analysis. Lane 2 and lane 4 are DNA from fetuses affected by the severe form of alpha thalassemia. You can see that in the severe form the normal alpha globin bands are absent.

Prenatal diagnosis of alpha thalassemia can be made at midtrimester, thus eliminating 20 weeks from a pregnancy doomed to produce a nonviable fetus. Diagnosis also prevents maternal toxemia and post partum hemorrhage, two complications that often occur with these pregnancies.

Some cases of beta thalassemia can also be diagnosed by digesting amniotic fluid cell DNA with restriction enzymes. However, the mutations that cause beta thalassemia are heterogeneous and at present most cases are still diagnosed by fetal blood sampling. New methods of DNA analysis are currently being developed which may facilitate diagnosis of this disorder.

In the near future, the recombinant DNA approach to prenatal diagnosis will be used for other genetic disorders. The genes affected by alpha-1 anti-trypsin deficiency and phenylketonuria have already been isolated, and it may soon be possible to diagnose these diseases with this technique.

Other diseases in which the gene involved has not been identified may also be diagnosed by analyzing DNA. Dr. Skolnick will have more to say about this.

For example, the genetic defect responsible for muscular dystrophy is not known, but a piece of DNA close to the chromosomal locus of the muscular dystrophy gene was recently identified in England. This DNA probe may soon provide a means of identifying the disorder in pregnancies at risk.

In summary, the recombinant DNA technique has provided a powerful tool for the diagnosis of genetic disorders. Sickle-cell anemia and thalassemia are the first of many hereditary genetic abnormalties to benefit from the new technology.

The ability to analyze DNA in this manner opens the door to a wide range of exciting possibilities. Within a few years a host of other inherited diseases may become amenable to diagnosis, prevention, and treatment.

Mr. GORE. Thank you very much.

I will hold questions until the rest of the panel has completed their presentations.

Our second witness is Dr. Mark Skolnick, associate professor of human genetics at the University of Utah College of Medicine in Salt Lake City.

Welcome to you and please proceed.

Dr. SKOLNICK. Thank you very much. I am not going to read my written testimony but I am going to try to comment a bit on what I have been hearing and how what I have written relates to that.

Mr. GORE. That is fine and without objection the prepared statement will be put into the record in full at this point along with the statements of our other witnesses.

Dr. SKOLNICK. Thank you very much.

We have talked about whether genetic engineering should occur in germ cell lines and this appears to be the strongest ethical issue.

Second, at what point is it appropriate to use recombinant DNA techniques in somatic cells. Finally, I am going to discuss a technique where no cells are injected with human DNA.

Dr. Kan has done extremely important work in establishing the use of genetic markers in a devastating disease. However, there still is the remaining ethical issue of abortion which is unacceptable to some populations.

I would like to show the very far end of this slippery slope of genetic engineering. That there is an area where I think, there are no visible ethical issues. Just benefit to society. Perhaps you can pick a hole in that argument. I would be delighted to go through that with you. But I can think of several genetic diseases where the use of genetic markers does not imply any difficult decision on the part of the individuals and its pure medical benefits are available.

I think that in addition to the horror stories of hybridizing a chimpanzee cell with a human cell, or injecting human cells in mice and having them passed on through the generations and so on, we should also discuss some of these very benign issues where recombinant DNA research is leading to a great advance in medical genetics.

Specifically following on the idea that was suggested by Dr. Kan's research with the hemoglobinopathies, myself and three colleagues proposed that the paucity of genetic markers which is responsible for so few of the human diseases being mapped could be overcome by the use of recombinant DNA research and the idea was simply to take fragments of DNA, the entire genome of human DNA, fragment it with restriction enzymes, clone them in plasmids and look at them one at a time and see which of them revealed multiple band patterns, like Dr. Kan showed on his slides.

If they did reveal multiple band patterns we could use them as signposts. For example, to return to the illustration earlier of the stretch of yarn from here to Baltimore and back, imagine trying to find things on that stretch of yarn if there were no street indicators.

The first step in understanding where genes are is to develop a set of signposts so that you can say this gene is with this signpost and this gene is with this signpost.

Now, of the 2,500 known genetic diseases listed in the "Mendelian Inheritance of Man," very few of them, a handful, several handfuls at most, have been mapped. Now that a number of signposts have been created with recombinant DNA, research is bursting forward and I predict that in 2 years there will be adequate signposts that genes can be mapped by doing a family study. This involves taking a large number of individuals related to each other, studying them, looking at the pattern of disease in that family and seeing which of these signposts has the same pattern.

So if two boys get the disease and two of their children get the disease, we can follow one of these particular signs, which could be the A blood group of the ABO system or it could be Rh minus of the Rh minus system. These are signs that we have known about, or we can follow any one of these arbitrary markers that are being developed now. Then we can assign that gene a position on the map.

This is extremely important. It could give us some ideas about potential therapies, be they conventional therapies or gene therapies. It could give us some idea of the defect.

It is important to know that for most genetic diseases we do not know the underlying defect. Therefore, we cannot clone the gene and go into the whole gene therapy mode or whatever other modes of understanding cloning the gene would get us, whether it is producing a biochemical factory in a bacteria or using conventional techniques.

So the best we can do is to try to predict the presence of the disease and that is the significance of genetic markers.

So, I think in several years and I mean 2 or 3 years, not 10 or 20, there will be enough genetic markers so that a large number of genetic diseases can be mapped and then in the next one or two decades we will see hundreds of these 2,000 diseases being mapped, such as muscular dystrophy which has been mapped recently.

As these diseases are mapped, we will then have the ability to predict which offspring will inherit the disease by studying a family. And a big difference in the use of genetic markers from a conventional diagnostic tool is medicine and diagnostic tools are done on individuals and with genetic markers you have to see the pattern in the parents, the pattern in the children and occasionally in more extended relatives. And from that, say an affected relative who received a certain marker you can predict whether the next relative down the line will receive the marker or not.

Mr. GORE. Now, what you are doing, in other words, is developing an understanding of the patterns which are associated with specific genetic markers and then you are inferring the presence of a specific marker if it always occurs in a particular pattern or near a particular pattern?

Dr. SKOLNICK. By its neighbor. You find out which marker a gentic disease is next to and then even though you have no sign of the presence of that disease by following the marker in families you can predict who inherited that gene and who didn't. Especially for late age onset diseases this is very important. It allows us to predict the future.

Mr. GORE. Now, why would it be limited to families? Presumably you might begin to discern patterns that were common to unrelated individuals?

Dr. SKOLNICK. That has occurred. That is called association with a marker. Association occurs if a particular letter of the alphabet at that marker locus is always associated with the disease, the general finding will be that, say, we have a disease linked to the ABO blood group. In one family it will have A on the chromosome that is carrying the defective gene. In another family B and in another family O. So it is important to find out which letter is diagnostic in that family and this is an important consideration in the sickle cell story.

There is an association but it is not 100 percent so you can do association studies but it is better to do linkage studies.

I hope Dr. Kan would agree with that. There is some debate in any case.

Mr. GORE. I am trying to understand what you are saying. I want you to correct me if I am way off base but what I keep thinking of is satellite photography. It would seem ludicrous to think that we could look at the whole land surface area of the Soviet Union, yet by learning to associate particular activities with concrete bunkers and silos and so forth and so on, we develop a great deal of confidence that in fact we can survey the entire terrain of the Soviet Union and look for specific patterns with which we relate the presence of a particular kind of missile.

Is that a wild analogy?

Dr. SKOLNICK. I think the analogy is good. We are trying to make a map of the genome as opposed to the map of the Soviet Union. Hopefully, it will have greater use for mankind than the map of the Soviet Union. But the silo changes form each time.

In other words, in one case the disease will follow with A. In another case it will follow with the B form of the marker. So there is no single pattern.

I must correct myself. When you know the genetic defect you can, in some instances, find a pattern that is caused by that different gene. So in one of the hemoglobinopathies now there is a specific pattern that is diagnostic for that disease. There is a restriction fragment that only occurs with that disease.

But in general, when you are mapping neighbors and following neighbors you have to know more. Say there are two cars in the garage being the two chromosomes and the idea is to find out which of these cars has the defective engine, this is the defective gene and you have to establish that in each family.

Say there is a Volkswagen and a Lincoln in every garage. In one case the Volkswagen will have the bad engine and in another case the Lincoln will. You just have to decide which gene is carrying the defect, which chromosome is carrying the defect in each family. It is not a case that always Volkswagens have bad engines and always Lincolns have good ones.

So it is a marker that is family specific.

Now, there are three examples that I would like to give of use of genetic markers. Again I claim that they are all noncontroversial and that none of them suggest abortion as an appropriate option and they all have simple therapies. The first is hemachromatosis. This is an iron storage disease where the body takes up more of the normal dietary iron than it normally takes up. We normally absorb one-third of our dietary iron and reject two-thirds and people with hemochromatosis absorb all the iron, essentially, that their body receives and they end up with rust in the body.

The cells overload with iron, the liver, the heart and other organs are affected and the person will eventually die of liver disease, liver cancer, diabetes, arthritis, heart disease and can suffer impotency.

This is a late age onset disease. Women are somewhat protected by having children and by menstruating they lose iron from the body and so they build up iron more slowly and have the disease at a later age.

By associating a genetic marker with this, HLA, in this case not a recombinant DNA marker, we were able to show that this is not a rare disease but it is the most common recessive disease known to man and that the chances are that one individual in this room who was here earlier today was affected with this disease and does not know it.

Approximately 1 million Americans are affected with hemochromatosis.

Mr. GORE. Is this what the television commercial describes as iron deficiency anemia?

Dr. SKOLNICK. This is exactly the opposite. This is loading up on iron to the point where you turn yellow and rust.

Mr. GORE. OK.

Dr. SKOLNICK. The cure for it is fantastic. All you have to do is become a blood donor. Your blood is rich in iron. By giving blood, you lose iron. The body then draws iron out of the cells to make more blood and if you are caught early enough before you have irreversible damage to your organs it is a totally curable disease and, as I said, about 1 million Americans are affected with this.

This does raise an ethical issue. I don't think anybody would disagree that this is the most pure form of treatment possible. There are no drugs. There are no abortions. There is no issues. The ethical issue is why are these 1 million Americans not being screened for hemochromatosis and having their lives saved.

I think a restructuring of our social system is required. The way we handle medicine is going to be one of the major consequences of recombinant DNA technology.

Two other examples are colon cancer and Wilms tumor. These are both diseases where we are searching for a marker, but even without a marker by looking at clusters of these diseases in families if we find the little colonic polyp that will eventually become a colon cancer and we have found 40 of these in high risk colon cancer families, we can remove it and essentially cure the colon cancer before it occurs and, again, this is the use of genetic technology because we say individuals with relatives with colon cancer need to be screened.

If we can find the genetic marker that can map colon cancer, we can know which individuals are susceptible. This screening is painful, it is expensive and it should be avoided in the individuals who do not carry the gene and it should be done more regularly by individuals who do carry the gene so we would be able to narrow down our scope for both colon cancer and Wilms tumor if we had a DNA marker. We are searching for those.

These are three examples. In two cases you would remove the pretumorous lesion or the young tumor and in hemochromatosis, simple phlebotomy would allow us to greatly alter the lives of those individuals and it is a clear use of genetic markers in medicine.

My conclusion is that one of the major problems is that our social institutions and medical practices are not geared toward the genetic discoveries that are about to follow from recombinant DNA research. We have 2,000 of these diseases, half of which will be mapped, say, in 10 or 20 years, and an entirely different type of medicine will be required, a predictive medicine. This prediction, in some cases where the individual's moral framework and the severity of the disease are appropriate will result in abortion.

In other cases it will require therapy, sometimes simple such as blood drawing, sometimes more complex. Each disease will pose its own issues.

But what is not well suited is that insurance companies will not pay for genetic screening now. Hospitals are not particularly structured to this approach. They are structured to waiting until someone has irreparable damage and then doing heroic, expensive operations, surgery and chemotherapy of cancer cases, whereas, prevention of cancer would be a much more appropriate formula. And doctors are not used to treating families.

People don't have the mentality now of using markers, treating a family, that health is a familial problem, and if we start thinking about our health problems you will, in general, find a relative who has similar health problems. We are discovering more and more genetic components of common diseases and I think one can find a genetic component in most common diseases. Even in infectious diseases there are genes that make some of us susceptible to infections and others resistant.

So my conclusion, then, is that there are some very straightforward applications of recombinant DNA to our health. There are now a million Americans that could be screened with genetic markers for hemachromatosis. Many more millions of individuals will be eligible for screening programs as these genetic diseases are mapped. And one thing that this committee should certainly explore is how our society is going to handle this great change in our medical care.

I'd like to end with a few other comments about what other speakers have said. One is we have been told not to worry about certain types of genetic engineering because some of the traits people would be interested in selecting for are multigene traits and I am not sure I agree with this.

Recently, an individual, Dr. Bodecky, has isolated statistically a gene for verbal capabilities among families and there may be similar genes which may be attractive for selection. So I am not sure that everything is so multigenetic and in the future problems may arise.

The other thing I'd like to say is that recombinant DNA is not new. There are living bacteria with human insulin genes in them that we in the scientific community have nothing to do with. And it is now believed that animals regularly exchange genetic material in evolutionary time, that there is crossing of genes from one species into another simpler life form and then across through the gut into another species and then reintroduced into that species.

And the final thing we have to keep in mind is that what we are discussing is a change in the human gene pool. By curing disease and allowing individuals who would have died to live, you are taking genes which normally are selected of in the gene pool and allowing them to stay in the gene pool. So if we are to have any far range view of what we are doing, looking at thousands or hundreds of thousands of years in the future, this problem will have to be faced.

And finally, this is an international problem, not a national problem. The last time an attempt was made to legislate recombinant DNA in this country, it merely set our scientists behind. It caused a number of them to take sabbaticals in Switzerland and I don't think simple solutions on a national scale will be useful.

Thank you.

[The prepared statement of Dr. Skolnick follows:]

DIAGNOSTIC USES OF GENETIC MARKERS

Testimony to the Subcommittee on Investigations and Oversight
of the Committee on Science and Technology
U. S. House of Representatives

by

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Genetic markers have been used for several decades to map diseases to the human genome. Unfortunately, there were not a sufficient number of them for a large number of diseases to be mapped, and they were not polymorphic enough to be generally useful. The advent of recombinant DNA technology has opened up the possibility of developing a genetic map saturated with restriction fragment length polymorphisms (RFLPs), as suggested by Botstein, White, Skolnick, and Davis (1980). In this testimony I will define what a genetic marker is and how they are used. I'll then describe how the new markers, RFLPs, can be found, the current status of their development, and how many will be needed to entirely map the human genome. I will describe their use in discovering where a disease causing gene is located, and finally discuss three cases of the application of genetic markers in a clinical setting. None of the three cases I will present requires a discussion of the issue of abortion of abnormal fetuses. This is an important and delicate issue which my colleague, Dr. Y. W. Kan, will address in his description of prenatal detection of hemoglobinopathies (Kan and Dozy, 1978). I would like to stress in my testimony that genetic markers can be useful in preventing disease in cases where there is no apparent ethical issue.

Genetic Markers

A genetic marker refers to an inherited trait, such as the ABO blood group or blue or brown eyes which can be followed in families. Until recently, these markers were limited to electrophoretic charge differences or antigenic differences in proteins and in differences in floresence in chromosome bands. Several dozen were available for use in gene mapping, but they were far too few for human gene mapping to be a systematic endeavor. The first problem in gene mapping is discovering where a gene is located, that is what marker is an appropriate signal for that gene on the genetic map. If the genetic defect is known, the gene can be cloned and a RFLP near it revealed, as Dr. Kan has done for sickle-cell anemia. But for most genetic diseases, the defect is not known and we must search for an appropriate marker, that is, one must map the location of the disease. Several hundred individuals in families with the disease must be studied with a battery of markers until we discover which marker follows the same inheritance pattern as the disease. The disease is then said to be mapped to the marker. I wish to emphasize that these genetic markers are not related to the etiology of the disease, but are "genetic neighbors" which travel with the disease as it is passed from generation to generation.

RFLPs

The problem with the above strategy has been that the battery of markers did not exist. Botstein et al. (1980) described a method of screening arbitrary clones of human DNA to look for heritable differences in DNA sequences which would be revealed as different lengths of DNA when the chromosome was cut with an enzyme which recognizes a specific sequence, or technically described as Restriction Fragment Length Polymorphisms, or RFLPs.

The strategy has proven successful (Wyman and White, 1980); Schafer and White, 1982). There are now numerous laboratories searching for such polymorphisms, and as of June, 1981, there were already 25 new DNA polymorphisms reported (Skolnick and Francke, 1982). Today, there are an estimated 70 in existence and new polymorphisms are being developed on a weekly basis. Bishop, Cannings, Skolnick, and Williamson, (in press) estimated that 400 markers would need to be discovered before an evenly spaced set of 80 could be developed as a primary mapping set. At the current pace, this will occur in several years. We should then see an explosion of activity in human genetics as the more than 2,000 known genetic diseases (McKusick, 1978) are mapped. This will be accomplished by studying a number of families with genetic markers. If one has a suspicion as to the nature of the genetic defect, a particular marker for that gene can be studied. But in general a battery will have to be studied. Once a gene has been mapped, if the markers are not informative enough, more markers in the region can be sought until the disease gene is flanked by several informative markers on either side.

Use of genetic markers

There is often confusion between a genetic marker and a normal diagnostic marker for a disease. We are used to the situation where only the affected person has to be tested, and a yes/no answer is given. With genetic markers, a family must be tested. Using the ABO blood group as an example, if a disease is linked to the ABO gene, in one family it may be linked to an "A" allele, in another to a "B" allele, and in another to an "O" allele. So the family must be studied to see which allele of the marker signals the presence of the gene in that particular family. If the affected parent has the same allele for the marker, then it will be useless in that particular family. Therefore, we really require multiple markers, and we would want each marker to have as many variations as possible--technically speaking, to be as polymorphic as possible. This will insure that we can detect the origin of the marker allele in a child and decide whether or not the child carries the disease in question.

Hemochromatosis

The first application I would like to discuss is hemochromatosis, the most common abnormal recessive genotype known. Individuals with hereditary hemochromatosis absorb more dietary iron than normal individuals and after many years of accumulation there is considerable organ damage, especially to the liver. Affected individuals may suffer from liver cancer, diabetes, arthritis, heart disease, and/or impotency. Often, hemochromatosis will not be known as the cause (Cartwright et al., 1979). Recently, by analyzing families with the disease with a very informative genetic marker, we were able to understand the genetic basis of hemochromatosis and show that it is a very common disease (Kravitz et al., 1979; Dadone et al., 1982). In fact we estimate that about 1 million Americans have the affected genetic constitution (carry two abnormal genes). In addition one out of seven are gene carriers. If they marry another gene carrier, one quarter of their children will be affected. Most individuals don't know that they are affected and indeed show no symptoms until there has been excessive organ damage. But the disease is readily curable; by becoming regular blood donors, affected individuals can rid their bodies of excess iron and never develop symptoms. These individuals can be recognized by an elevation of their saturation of an iron transport protein and by use of the genetic marker near the gene. In this case genetic analysis with a marker has provided the basis for the elimination of a major cause of human suffering. There are also no ethical issues raised. It is up to society to recognize the importance of early detection and prevention of this disease.

Colon Cancer and Wilms' Tumor

The picture is more complex for Colon Cancer and Wilms' Tumor. Where the vast majority of hemochromatosis is genetic and occurs in families, only a fraction of these and other cancers occur in families. Their similarity with hemochromatosis is that screening is effective. It is also expensive and involves some risk. Wilms' Tumor is a childhood kidney tumor(Strong,1976; Matsunaga,1981). In some cases a band of chromosome 11 is deleted. In other cases, it occurs in families, although its occurrence is dispersed. We are studying a family, where there is no Chromosome 11 deletion to follow. We are trying to prove that another genetic marker on chromosome 11 will serve the same purpose. If our study succeeds, we will be able to identify which of the dozens of young children in this genealogy need to be studied and which children can be spared the pain, expense, and danger.

It's imperative that these children be screened as five of the six affected individuals in this family died from the disease.

Colon cancer is the final example I will offer. If it is detected through symptoms, it's often too late. If we could predict who was liable to develop colon cancer and screen them before they are symptomatic, removing any adenomatous polyps which are found, we can prevent the disease from ever developing. We cannot convince the entire population to regularly have their colons examined. However, we have studied 180 people in high risk families and found 41 with adenomatous polyps, which have been removed (Burt et al., in press). Although not all of these would have developed into colon cancer, many would have. We are using these families to try to map colon cancer to a genetic marker which would allow us to limit our screen to the truly high risk individuals.

Conclusion

Human genetics offers many challenges to our current social and medical practices. It offers the possibility of predicting which individuals will develop which diseases, and will eventually leave society with the heavy responsibility of acting on that knowledge. Much of this predicting ability is based on the creation of a genetic map of man, which will certainly be one of the major achievements of our society in the next several decades. In some cases, the knowledge of map location will lead to an understanding of the disease mechanism and open the way for new treatment modalities, among them, gene therapy.

In other cases, disease mechanisms will escape us, and we will be left with the ability to predict a disease in an individual. Here again there is a dicotomy. In some instances knowing who is affected leaves us with unpleasant options such as family limitation, abortion, or caring for a very sick child with little future. In other cases, there are simple measures which can overcome the genetic predisposition. The universal aspect of our new genetic tools is the change in the practice of medicine which they dictate. Medicine is becoming a science of prediction and prevention rather than diagnosis and treatment. This will have an obvious social impact--longer and healthier lives. It also will require a reorganization of health care whose main forces--insurance companies, hospitals, and doctors-- are all tuned to treating late stage diseases in individuals. Much of our national health care budget needs to be reorganized to predicting and preventing diseases in families. Is it better to treat hemochromatotics for liver cancer, heart failure, and diabetes after they have suffered irreparable organ damage, or set up a national screen for the disease? Insurance companies in general won't pay for screening of genetic diseases, even in high risk families. Such screening is also not in the interest of hospitals. Doctors often fail to perform follow-up studies on the relatives of individuals with genetic diseases. There is a revolution in our ability to predict who will be affected with what disease. It is not too soon to begin considering what institutional changes this revolution implies.

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Construction of a Genetic Linkage Map in Man Using Restriction Fragment Length Polymorphisms

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SUMMARY

We describe a new basis for the construction of a genetic linkage map of the human genome. The basic principle of the mapping scheme is to develop, by recombinant DNA techniques, random single-copy DNA probes capable of detecting DNA sequence polymorphisms, when hybridized to restriction digests of an individual's DNA. Each of these probes will define a locus. Loci can be expanded or contracted to include more or less polymorphism by further application of recombinant DNA technology. Suitably polymorphic loci can be tested for linkage relationships in human pedigrees by established methods; and loci can be arranged into linkage groups to form a true genetic map of "DNA marker loci." Pedigrees in which inherited traits are known to be segregating can then be analyzed, making possible the mapping of the gene(s) responsible for the trait with respect to the DNA marker loci, without requiring direct access to a specified gene's DNA. For inherited diseases mapped in this way, linked DNA marker loci can be used predictively for genetic counseling.

INTRODUCTION

Although it is possible to detect linkage among simple Mendelian traits in humans, no method of systematically mapping human genes has been devised, largely because of the paucity of highly polymorphic marker loci.

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The advent of recombinant DNA technology has suggested a theoretically possible way to define an arbitrarily large number of arbitrarily polymorphic marker loci. In this paper, we discuss this general approach to the construction of a human genetic linkage map using recombinant DNA probes to define marker loci which are polymorphic in DNA sequences; a subset of such DNA polymorphisms can readily be detected directly as differences in the length of DNA fragments after digestion with DNA sequence-specific restriction endonucleases. These restriction fragment length polymorphisms (RFLPs) can be easily assayed in individuals, facilitating large population studies. Small volumes of peripheral blood should provide sufficient lymphocyte DNA for analysis.

RFLPs should be inherited as simple Mendelian codominant markers; this can be verified in family studies. Linkage relationships among RFLPs can be established using pedigree analysis [1–3]. Evaluation of many DNA marker loci should allow the establishment of a set of well-spaced, highly polymorphic genetic markers covering the entire human genome. Since the RFLPs are being used simply as genetic markers, any trait caused wholly or partially by a major locus segregating in a pedigree can be mapped. Such a procedure would not require any knowledge of the biochemical nature of the trait or of the nature of the alterations in the DNA responsible for the trait. No specific gene isolation is required, and the RFLPs can be random sequences functionally unrelated and physically distant from the DNA encoding the locus of interest. In fact, on the average, the physical distance represented by 1 cM (.01 recombination fraction) is about 1,000,000 base pairs (1,000 kilobases [kb]) [4]; we suggest the need for linked markers about 20 cM apart (i.e., 20 million base pairs).

Such a mapping procedure will also allow better definition and substantiation of models of inheritance for the many familial traits which have been refractory to simple genetic analysis in humans. The usefulness of a tightly linked polymorphic locus in resolving modes of inheritance has recently been demonstrated [5].

RESTRICTION FRAGMENT LENGTH POLYMORPHISM (RFLP): DEFINITION

DNA restriction enzymes (see [6] for review) recognize specific sequences in DNA and catalyze endonucleolytic cleavages, yielding fragments of defined lengths. Restriction fragments may be displayed by electrophoresis in agarose gels, separating the fragments according to their molecular size. Differences among individuals in the lengths of a particular restriction fragment could result from many kinds of genotypic differences: one or more individual bases could differ, resulting in loss of a cleavage site or formation of a new one; alternatively, insertion or deletion of blocks of DNA within a fragment could alter its size. These genotypic changes can all be recognized by the altered mobility of restriction fragments on agarose gel electrophoresis.

Fragments encoding *specific* sequences from within a large and complex population of DNA fragments can be detected by hybridization using the method of Southern [7]. The DNA from an agarose gel is transferred onto nitrocellulose paper and hybridized with radioactive probe sequences. Recently, the use of probe sequences of very high specific radioactivity has permitted the identification by this method of single-copy sequences in mammalian DNA [8]. This powerful new technology makes possible the identification of variants from within a specific region of the genome, using digest of total human DNA.

Restriction endonuclease fragment polymorphisms have also proven useful in the genetic analysis of chromosomal markers in yeast. Three groups [12–14] discovered RFLPs in their systems of study. Six of eight EcoRI restriction fragments encoding tyrosine tRNA were mapped using RFLP analysis [13, 15]. An RFLP at a particular tyrosine locus (*SUP4*) was shown to be generated by the presence or absence of a 5.8-kb repetitive DNA segment [14]. By use of a restriction site polymorphism, recombination was examined, and the RFLP was subsequently used to map the DNA locus [12]. RFLP analysis has also been applied to genetic mapping in the nematode worm *Cenorhabditis elegans* (Hirsch, personal communication, 1979).

RFLPs IN HUMAN DNA

More recently, RFLPs have been discovered in human systems. In the region of the human *globin* genes, a heterozygosity for a PstI restriction site has been found within the intervening sequence of the *γ-globin* gene among recombinant DNA clones [16]. Apparently, the two chromosomes of the individual from which the DNA was isolated were heterozygous for this marker. This was confirmed by examination of a Southern transfer of DNA from the individual. HpaI fragment length polymorphic variants associated with sickle-cell traits have also been found [17]. Although most human *β-globin* genes were present on a 7.6-kb HpaI fragment, among individuals of African origin, *β-globin* genes were also found on 7.0- and 13.0-kb HpaI fragments. Of individuals with the *hemoglobin +S* allele, 87% were found to have the 13.0-kb variant fragment. This linked RFLP has been used to diagnose sickle-cell trait in utero [17]. More recently, the abundance of RFLPs associated with the *β-* and *γ-globin* regions have been examined [18, 19]. Among 60 individuals, Jeffreys found one rare and two frequent polymorphisms.

GENETIC MAPPING WITHOUT SPECIFIC GENE ISOLATION

The above RFLPs were recognized by their relationship to the DNA sequence for a gene of interest. These experiments could not have proceeded without prior isolation of the specific gene's DNA. We note, however, that for the more general purpose of mapping genetic loci, RFLPs need not encode the gene of interest, but only be sufficiently nearby to display genetic linkage. This is extremely important, because a recombinant DNA probe need not reveal a restriction fragment containing part of the gene of interest to be useful; that is, one does not have to "isolate the gene" to map it. If a substantial number of polymorphic regions can be identified (and we estimate that 150 will eventually be required), then all genes will be linked to one or another of the regions containing RFLPs and can thereby be mapped.

MAKING THE RFLP MAP

The demonstration of a heritable and detectable RFLP at the *β-globin* locus implies that the genetic mapping scheme based on linkage in family studies of randomly derived RFLPs is possible in principle. It is less clear, however, how difficult it will be to find usefully polymorphic loci and to establish linkage relationships in practice. To address these issues, we must answer a series of questions, many of which can have interdependent and complex answers. Four interrelated questions must be answered:

(1) How many markers are needed? (2) How polymorphic must each marker be? (3) How many families are needed to establish linkage? and (4) How much polymorphism can we expect in the human genome?

For counseling purposes, the number of markers needed and the degree of polymorphism desired are unlimited: more and higher are always better. Although loose linkage to a slightly polymorphic marker is better than no linkage, the tighter the linkage, the more accurately one can predict genotypes, and the higher the degree of polymorphism, the more often one will have informative families necessary for counseling. For the purpose of construction of a genetic linkage map, we can be less demanding and more precise, although here, too, the need for polymorphism and useful marker loci can never be totally fulfilled.

Individuals and lineages spanning multiple generations will be selected from large pedigrees. The restriction fragment fingerprint resulting for each probe, from each individual, will be recorded and analyzed for linkage. The pedigrees under study will already have been typed for HLA, red cell antigens, and isoenzymes. Standard LOD score analysis in pedigrees, explained below, will determine linkages between the probes, and between each probe and other chromosomal markers.

Mostly, we expect RFLPs to be inherited as Mendelian codominant alleles. These might simply be the result of single-base pair changes, although other possibilities can be imagined. Deletions, additions, and other local rearrangements should also manifest Mendelian inheritance. RFLPs within distant translocations, however, will reveal unusual inheritance, since the probe may be detecting sequences that, although homologous, are genetically unlinked.

Another interesting possibility is that RFLPs could result from the activity of DNA modifying enzymes [20]. In this case, pedigree analysis would show us the linkage relationship of the modification genes. Furthermore, these polymorphisms might not give the expected codominant phenotype, but will be expressed as either true dominants or recessives, depending on whether the gene is structural for a modifying enzyme or regulatory; and if regulatory, whether positive or negative. Furthermore, the activity of such a system might affect RFLPs detectable with several probes, possibly known by mapped RFLPs to reflect sequences imbedded in separate linkage groups. In this case again, linkage relationships might yield apparently disparate results. The two described possibilities are distinguished by their dominance characteristics, rearrangements giving codominance, and modifying enzymes being either dominant or recessive. Other, even more complex, possibilities may exist.

Before considering our questions, we must briefly address the issue of how linkage data in humans are analyzed. As RFLPs are identified, they must be examined for a number of statistical properties by pedigree analysis [1–3]. To establish a map of markers, pedigree analysis will be used with qualitative traits (such as allele 1, 2, . . . , *n*). As diseases are studied later, quantitative traits such as cholesterol, weight, time to an event, or a combination of the above will also be considered. Models are fit by maximizing the likelihood of the parameters given the pedigree structure and the observations. Geneticists compare likelihoods of different models by calculating likelihood ratios. When the likelihood ratio is 1000:1, that is, the odds of one model are 1,000-fold greater than the odds of another, then the first is accepted compared to the

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latter. The $\log_{10}$ of the likelihood ratio (LOD score) as described by Morton [21], is usually reported. Thus a LOD score of 1 to 2 is "interesting"; 2 to 3, "suggestive"; and > 3, "proof" of the phenomenon in question.

How Many Markers Are Needed?

To answer this question, we must know how large the human genome is in genetic terms and how far one can be from a marker and still detect linkage. Renwick [4] has estimated that the human genome is 33 Morgans in length. Figure 2, from [22], shows that the expected LOD score for two linked markers in small family structures falls by an order of magnitude between $\theta = .1$ and $\theta = .3$, where θ is the recombination fraction. Therefore, a search for linkage will be very inefficient at greater values of θ. For this discussion, an equivalence between Morgans and recombination fraction is assumed, which is approximately true within this range of values. We will pick $\theta = .2$ as the maximum distance desired between RFLP marker loci which will still allow linkage to be detected. To map a new RFLP, a dominant gene for a disease, or a gene for a carrier trait, RFLPs spaced 0.2 Morgans apart will be sufficient to guarantee that a gene is detectably linked to an RFLP locus at a distance no greater than $\theta = .1$. At this distance, and without further dividing the 33 Morgans into individual chromosome

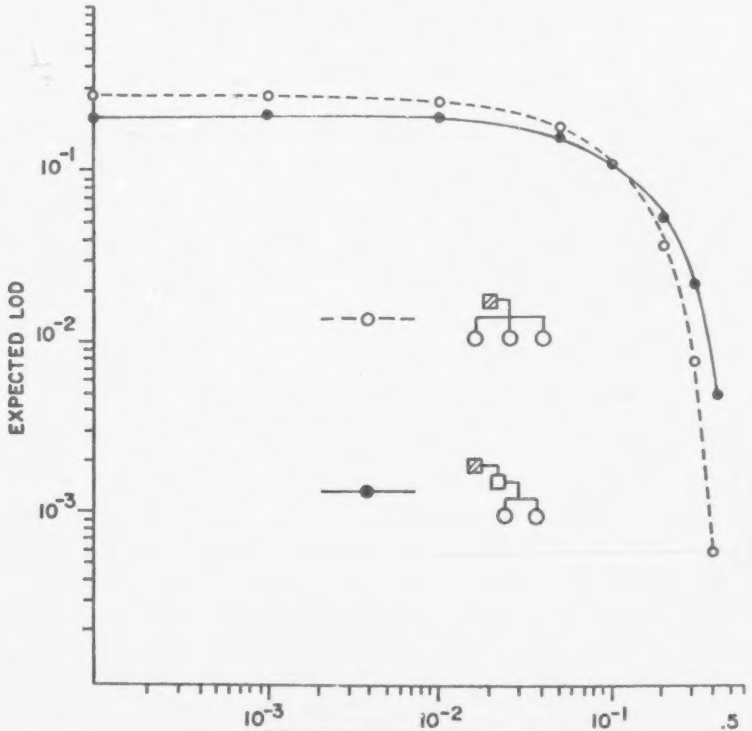

FIG. 2.—Expected LOD score as a function of recombination fraction for two 4-member pedigrees

sizes, about 150 RFLP markers would be required. To create a map, more than 150 polymorphic probes (marker loci) must be isolated and tested and, occasionally, slightly greater than optimal distances will have to be accepted.

How Polymorphic Must Each Marker Be?

To simplify this discussion, we will imagine that we are examining for linkage a pair of loci which we will call the "index" locus and the "marker" locus. We will assume that the index locus contains a rare dominant allele which segregates in the family under study. The allele could be a disease trait or a rare allele of an RFLP locus. The marker locus is a polymorphic locus for which information for linkage studies is to be determined. We assume that all alleles at the marker locus are codominant, which is our expectation for RFLPs. Our assumption of rarity of an allele at the index locus is made only to simplify the discussion and is not a necessity for our analysis. The lineage of the rare allele at the index locus in the family under study is always clear by our assumptions. The question to be answered is: How does the degree of polymorphism at the marker locus influence the probability of detection of linkage to the index locus? Informativeness in this context is represented by the probability that a given offspring of a parent carrying the rare allele at the index locus will allow deduction of the parental genotype at the marker locus. Table 1 gives the mating types, their frequencies, and the probability of informativeness of an offspring for a marker locus, A_i, with n alleles and frequencies p_i.

TABLE 1

MATING TYPES, PROBABILITY THAT OFFSPRING ARE INFORMATIVE, AND FREQUENCY OF EACH TYPE FOR THE LINKAGE MODELS

Genotype of affected parent	Genotype of unaffected mate	Probability offspring informative	Frequency of mating
A_iA_j	A_kA_l	1.0	$2p_ip_j(l - p_i - p_j)^2$
A_iA_j	A_kA_i or A_kA_j	1.0	$2p_ip_j(1 - p_i - p_j)(2p_i + 2p_j)$
A_iA_j	All homozygotes	1.0	$2p_ip_j \sum_{i=1}^{n} p_i^2$
A_iA_j	A_iA_j	.5	$2p_ip_j \times 2p_ip_j$
All homozygotes	All genotypes	0	p_i^2

One can evaluate each marker locus for its polymorphism information content (PIC) by summing in table 1 the mating frequencies multiplied by the probability that an offspring will be informative. Under our assumptions, the expected value of PIC can be calculated as

$$1 - \left(\sum_{i=1}^{n} p_i^2\right) - \sum_{i=1}^{n-1} \sum_{j=i+1}^{n} 2p_i^2p_j^2$$

A similar index can be found in [49].

Both index and marker loci are considered in nuclear families, ignoring both the advantages and complexities of multigenerational studies which allow one to know the coupling or repulsion of disease and marker loci and, on occasion, the genotypes for loci with recessive or silent alleles. Multigenerational studies can increase the amount of information which can be derived from a marker locus, but they should not alter our basic impression of the value of a locus for linkage. Complications in the genetic model can make detection of linkage much more difficult and can reduce the PIC. Table 2 presents the PIC and number of alleles for 29 established codominant chromosomal markers. The calculations use gene frequencies in Caucasians. Under this formulation, there are four codominant loci which are highly informative (PIC > .5), fifteen are reasonably informative (.5 > PIC > .25), and ten are only slightly informative (PIC < .25). Loci with many alleles and a PIC near 1 are most desirable. Such loci will probably be essential if the kind of mapping method we propose is to become a practical reality.

How Many Pedigrees?

The number of informative families required can only be estimated. The precise pedigree structure and family size are relevant in determining this number. An analysis of this problem [22] has shown that the amount of information in a family study varies considerably with the precise structure of the pedigree; Thompson et al. quantified two

TABLE 2

PIC OF 29 CODOMINANT HUMAN CHROMOSOME MARKER LOCI IN CAUCASIANS

Locus	PIC	No. alleles	Population	No. subjects	Source
HLA-A	.976	12	European	...	[23]
HLA-B	.976	16	European	...	[23]
MNSs	.638	4	English	1000	[24]*
Rh	.580	6	English	154	[25]*
AP	.448	4	English	597	[26]
TC II	.400	4	Caucasian	131	[27]
GPT	.382	3	Caucasian	528	[28]
Jk	.375	2	English	201	[29]*
P	.375	2	English	1166	[30]*
Fy	.368	2	English	1166	[30]*
Hapt	.367	2	English	218	[31]
GLO	.363	2	S.W. German	169	[32]
Pg	.359	2	Caucasian	931	[33]
CDA	.352	2	Caucasian	189	[34]
Bf	.342	3	Caucasian	158	[35]
Gc	.325	2	English	49	[36]*
PGM_3	.308	2	English	583	[37]*
PGM_1	.286	6	English	2115	[38]*
C3	.277	2	Norwegian	400	[39]
Amy_2	.171	2	Caucasian-U.S.	673	[40]
ESD	.162	2	European	867	[41]
ADA	.089	2	English	1353	[42]*
GALT	.087	2	S.W. German	195	[43]
UMPK	.086	3	Caucasian	386	[44]
KELL	.084	2	British	8767	[45]*
AK_1	.082	2	British-N. Ireland	1887	[46]*
Lu	.058	2	English	1166	[30]*
6PGD	.042	3	English-London	4558	[47]*
PEPA	.002	3	British	2283	[48]*

* Data compiled from: Mourant AC, Kopec AC, Domaniewska-Sobczak: *The Distribution of the Human Blood Groups and Other Polymorphisms*, 2nd ed. London, Oxford Univ. Press, 1976

well-known principles: multigenerational pedigrees are more useful than nuclear families, and large families give considerably more information than smaller families. The expected LOD score also varies with the recombination fraction. Figure 3 (from [22]) shows that an expected LOD score of 0.1 spans both the range of reasonable sibship sizes (2 to 8) and recombination fractions .3 to .0001. To establish a LOD score of 3.0, we would need 30 of these units; this translates into 300 individuals to establish a linkage at $\theta = .3$, and as few as 21 individuals to establish linkage in three 5-child families where tight linkage between the index and marker loci exists. These numbers can be decreased further if the nuclear families are linked in a multigenerational pedigree. The advantages of large genealogies can also be exploited further if the genealogy of untested family members is known and principles of sequential sampling are employed to determine which members should be studied. One excellent source of large pedigrees of known genealogical structure is the computerized data base created by the genetics group at the University of Utah, a file that contains seven generations of descendants of the Utah Mormon pioneers, who, because of large family sizes, often have descendants numbering in the thousands [50, 51]. This data base is also useful in the search for new markers in pedigrees where the known markers have been assayed. The numbers cited above (15 to 300 individuals) must be multiplied by a function of the reciprocal of the PIC of the marker locus used. For this reason, we are initiating our search for RFLPs in large Mormon pedigrees with genetic defects, which are already being analyzed for known chromosomal markers.

The above discussion emphasizes the interplay between sample size, degree of polymorphism of each marker locus, and recombination distance between the loci in question. In summary, we expect that a set of about 150 markers, each 0.2 Morgans apart, will be required, and that if their average information content (PIC) is .5, several

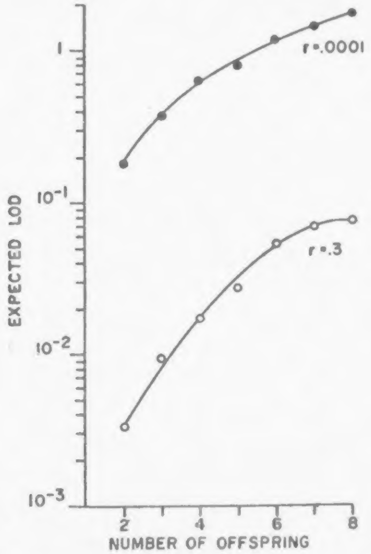

FIG. 3.—Expected LOD score for two recombination fractions (r) as a function of sibship size

hundred individuals, at most, will be necessary to establish linkage to any given index locus. During the process of mapping RFLPs, we need to make more extensive pedigree studies using RFLPs which are less polymorphic. If the number of subjects available for study is limited, a larger set of markers could allow one to reduce the number of individuals required. An expected LOD score of 3 will result from about 6,000 analyses (individuals × markers) over a wide range of marker densities [52].

The most efficient procedure in establishing RFLPs will be to study a small set of large pedigrees which have been genotyped for all known polymorphic markers (red cell antigens, isoenzymes, HLA, and chromosome-banding polymorphisms). All probes showing usable PIC values will be studied further to establish segregation and define linkage groups. RFLP markers will also be studied further for linkage with known markers. As the study develops, a set of RFLPs denoted R_{ijk} will emerge, where i denotes the linkage group (chromosome, if known); j, the locus within the chromosome; and k, the specific fragment at the locus. Many fragments at a locus made with different restriction enzymes will be investigated. In addition, neighboring clones will be studied to expand polymorphism to an amount sufficient for linkage studies.

Before RFLPs become a useful tool for mapping disease loci, the number of members of set R will be reduced. Some R_{ijk} will be unnecessary for initial screening, and efficiency dictates that a primary set, R', be established, eliminating some of the j sites, and for each site, some of the fragments. If linkage is not detected, the secondary set, R'', containing additional fragments at R' loci and additional loci, will be sequentially examined until linkage is established.

Once linkage is suspected, neighboring loci will be explored until the closest locus is found. One may expand the set of fragments at this locus by seeking neighboring fragments to increase polymorphism.

For some counseling purposes, we wish to find the closest RFLP to the disease locus which has unique alleles in both parents. Another possible approach is to try to find two RFLP loci which flank the disease locus on the genetic map. Such flanking markers will greatly increase the certainty of genotype determinations used as the basis for counseling.

Estimates of the Frequency of Polymorphism in DNA

The above considerations lead us to the question of how much polymorphism to expect in human DNA. Although little is known about the frequency of DNA polymorphism in humans, several sources of information can be used to provide order of magnitude estimates, including determinations of base sequence divergence based on melting temperature depressions of reannealed DNA, and measurements of amino acid sequence divergence among proteins.

Estimates from the frequency of protein polymorphism. The frequency of polymorphism among 71 protein studies in European populations [53] was 0.28, suggesting that the minimum DNA sequence polymorphism must be at least 0.28 base changes per 1,000 base pairs, the size of the average gene. Assuming that visible electromorphs represent about one-third of the nucleic acid sequence changes and that many third-base changes are not reflected in corresponding amino acid changes, we can estimate the frequency of DNA sequence polymorphism to be about 0.001 per base pair among protein-coding sequences. This sets a lower limit for the amount of base-sequence polymorphism, since sequences found as mRNA have been shown to diverge more slowly than the bulk of the single-copy DNA [54].

Estimates from the depression of the melting temperature of reassociated DNA. Divergence of nucleic acid sequence between related species has also been determined by measurement of the relative depression of the denaturation temperature of DNA that has been melted and reassociated with DNA from a heterologous species. However, only one attempt has been made to determine the extent of polymorphism within a mammalian species by heteroannealing DNA from separate individuals of the same species [55]. This study indicates that the DNA-sequence polymorphism due to single-base changes between an individual wild mouse and an inbred C57B1 mouse is low. In fact, no melting temperature depression was observed, from which one can conclude that the resultant heterozygosity was probably less than .5% (Britten, personal communication, 1979), corresponding to a DNA polymorphism frequency of 1.1%. This conversion from degree of heterozygosity to degree of polymorphism is approximate and conservative: approximate in that it uses a formula [56] which assumes no selection, and conservative in that we have defined polymorphism as requiring a minor allele with a frequency of at least 10%, as less polymorphic loci are not of interest for our purposes. This suggests an upper limit to the extent of DNA polymorphism in mammals due to base-pair changes.

RFLP calculation. Assuming an average of the above estimates of polymorphism for human DNA due to base-pair changes, we can calculate the probability that a restriction fragment will be polymorphic: If we let p be the fraction of nucleotide sites showing significant polymorphism (frequency of the minor allele greater than 10%); n, the number of nucleotides in the restriction enzyme site; and S, the probability that a given restriction site is not polymorphic, then $S = (1 - p)^n$. Taking into account such parameters as average restriction fragment length, AT to GC ratio, and appearance of new sites as well as disappearance of old sites, Upholt [57] was able to show that f, the fraction of restriction fragments showing no polymorphism, will be approximately equal to $S^2 (2 - S)$. If we assume a nucleotide site polymorphism of 1.1%, the upper limit suggested by the mouse study described above, then the probability that a restriction fragment defined by a four-base enzyme would also be polymorphic is 12.3%. Using the lower limit for polymorphism suggested by the protein electromorph studies, 0.23, the probability of restriction fragment polymorphism becomes 0.34%. The corresponding probabilities for fragments defined by restriction enzymes which recognize six-base sequences are 17.7% and 0.50%. Even though the probability per fragment of polymorphism is somewhat less for the fragments defined by the four-base enzymes, they should be more useful in revealing polymorphism due to single-base changes in DNA, since there are approximately eight times as many base fragments produced per unit length of DNA.

Polymorphism due to insertions and deletions. Another possible source of polymorphism other than single-base-pair changes is the insertion or deletion of blocks of DNA. These DNA polymorphisms would be underrepresented in the above estimates, but will serve to increase the amount of DNA polymorphism. In yeast and

Drosophila, RFLPs have been discovered which are due to such alterations. In these species, the mobile DNA segments are moderately repetitive [14, 58]. The frequency in humans of DNA polymorphism from this source cannot yet even be estimated. Insertion and deletion of such mobile DNA segments could, however, also be a major mechanism for the generation of restriction fragment length variation in humans. The change in mobility of a restriction fragment due to insertion or deletion is unpredictable in advance. Insertions would increase the length of a restriction fragment if the inserted segment does not contain a restriction site or, possibly but not necessarily, decrease the fragment length if it does contain a restriction site. Similarly, deletions completely internal to the restriction fragment will decrease its length, whereas deletions, including one of the restriction sites, could either increase or decrease the fragment length depending on the size of the deletion and location of the next nearest restriction site. Deletion of the entire probed sequence would not be revealed and would have a recessive phenotype. The most diagnostic feature of insertions and deletions would be their pleiotropic effect on some restriction fragments generated by several restriction enzymes.

If mobile, repetitive DNA segments were found in human DNA, these could serve as a probe for loci likely to show polymorphism. The mobile sequence could be cloned and used to screen the human genomic library. Isolation and analysis of the sister DNA segment clones should reveal the presence of adjacent, single-copy sequences. These then could be used as probes of DNA from individuals to determine whether the repetitious segment is mobile from the new locus, thereby defining a new polymorphic site. Although the number of fragments examined is the important parameter in discovering RFLPs due to single-base changes, the length of DNA screened is the most important factor in the case of insertions and deletions, since many different restriction fragments, defined by different enzymes, will reveal the same insertion or deletion.

SOURCE OF RECOMBINANT DNA PROBES DEFINING RFLP LOCI

To find polymorphisms, we must be able to identify specific and unique regions of the genome. The recent development of recombinant DNA technology permits the cloning in *E. coli* of individual segments of the human genome. These DNAs can be labeled with radioisotopes to high specific activities and used as hybridization probes of DNA from individuals, being digested with various restriction fragments from specific regions.

Two libraries of human recombinant DNA have been constructed by two quite different methods, each with properties relevant to this purpose. One library was constructed from the DNA of the entire human genome [17], using a bacteriophage vector. The inserted segments in these recombinant phage range in size from 15 to 20 kb. A second library of human DNA sequences was constructed from messenger RNA (L. Villa-Komaroff, personal communication, 1978). To prepare this human library, messenger RNA was enzymatically copied into DNA (cDNA) inserted into a plasmid vector. These segments of messenger sequences are each about 500 base pairs long. The phage library contains segments representing the DNA sequences of the entire human genome, and the cDNA library reflects those human sequences transcribed into messenger RNA, providing an opportunity to characterize each set respecting polymorphism.

The phage clones with their large inserts will reveal many more restriction fragments than the much smaller inserts of the cDNA clones. Most of the long segments, however, are likely to contain interspersed repetitive sequences [59] which would hybridize to fragments from many different regions of the genome. The cDNA clones should mostly reflect gene sequences present in only one copy (or a few, see below) per haploid genome, but many represent DNA sequences which are more highly conserved and reveal fewer polymorphisms.

The liability of the large phage probes is that they generally will contain moderately repetitious sequences interspersed within single copy. There is evidence that the human genome, like most eukaryotic genomes, is organized with moderately repetitious sequences interspersed within the single-copy sequences [59]. Since the mid-repeat DNAs will hybridize to many fragments, presumably from many parts of the genome, the pattern of the Southern transfer becomes too complex for ready interpretation. However, the available evidence suggests that not all the single-copy human DNA contains short-period interspersed mid-repeat sequences; a fraction of the single-copy DNA should contain quite long (more than 10 kb) segments of DNA with no interspersed mid-repeat material. Preliminary results indicate that a reasonable proportion (1%–3%) of the phage clones contains no mid-repeat sequences, and the clones are usable as probes without further alteration [60]. These were discovered by screening the phage library with radiolabeled mid-repeat human DNA, selecting clones which do not hybridize.

Figure 4 shows that a locus can be substantially expanded by using the initial recombinant DNA sequence to probe the phage library for adjacent sequences, from which a new composite probe can be constructed. The procedure is called "walking" and consists of identifying successive, adjacent clones of recombinant DNA, orienting them by their restriction enzyme site pattern with the primary clone, and excising the mid-repeat sequences as indicated above. Additional steps can be taken, the new sequences each having their associated polymorphisms, until the desired degree of polymorphism is achieved. The combined set of subcloned, single-copy-only fragments from a specified longer primary sequence, containing no mid-repeats, constitutes a usable probe for that region.

REFINING MODELS OF INHERITANCE USING THE RFLP MAP

The resolution of genetic and environmental components of disease has evolved in the last decade into a well-formed discipline of genetic epidemiology. While the methods of analysis are still widely disputed [61, 62], many of the problems at least are agreed upon. A description of the genetic epidemiology of a disease must involve unraveling the model for the underlying genetic predisposition (endogenous factors); understanding the environmental contributions (exogenous factors); including the effects of chance, development, and age; and, finally, understanding the variability of expression of the phenotype.

In principle, linked marker loci can allow one to establish, with high certainty, the genotype of an individual and, consequently, assess much more precisely the contribution of modifying factors such as secondary genes, penetrance, and environment. Tightly linked markers (such as HLA) have been used to clarify genetic models

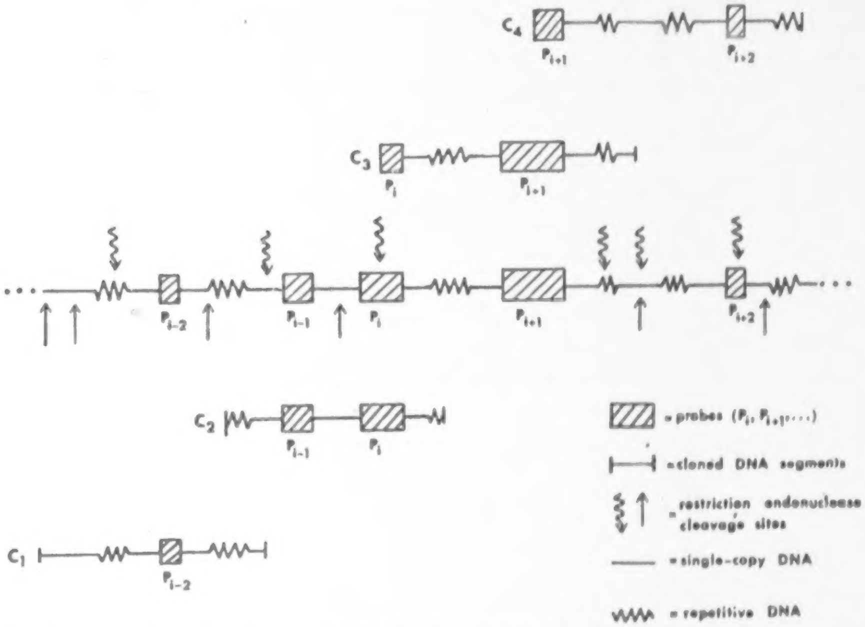

FIG. 4.—Expansion of probe p_i with neighboring probes p_{i-2}, p_{i-1}, p_{i+1}, and p_{i+2}. Probes are diagrammed in an intact DNA region with restriction cleavage sites indicated and also in homologous cloned DNA segments, C_1, C_2, C_3, and C_4, which may contain parts of some probes.

and improve recurrence risks [5]. This analysis simultaneously established the "recessive" genetic model and demonstrated linkage to HLA. Furthermore, studies of additional pedigrees failed to demonstrate heterogeneity in the etiology of the disease and suggested a disease frequency approximately 40 times greater than previously estimated [63]. The analysis also showed that one large, informative pedigree gave twice the information available in nine smaller ones.

However, since not all disease loci can be expected to be found in the HLA region, and since other markers, only slightly polymorphic, would not have allowed the discrimination necessary to resolve the genetic system, this approach has been severely limited. The intrinsic liabilities to the marker systems are compounded by heterogeneity, late age of onset, variable expressivity, environmental interactions, and other complications found associated with many important diseases. In fact, known markers have failed to provide linkage to important disease loci (such as Huntington disease). Because of these difficulties, only 2%–3% of known Mendelian disorders have been mapped.

As an alternate approach, substantial progress has been and is being made in determining the chromosomal location of many genes by the method of segregating human chromosomes from human:mouse fusion hybrids (see [64] for review). However, to map disease loci, this method depends upon knowledge of the biochemical defects at the cellular level. Since the biochemical basis for most genetic disease remains obscure, their loci are refractory to localization by the fusion approach or its variations.

DISCUSSION

The application of a set of probes for DNA polymorphism to DNA available to us from large pedigrees should provide a new horizon in human genetics. Recent applications of these methods, specifically to hemoglobinopathies [18, 19], have already provided major results. Once established, DNA polymorphisms will be useful for in utero assays, as has been shown for hemoglobin [18, 65]. This is important since, even when successful, current linkage studies provide markers which are generally unusable for preventive medicine because they cannot be assayed in utero, or because of only marginally informative polymorphism. With linkage based on DNA markers, parents whose pedigrees might indicate the possibility of their carrying a deleterious allele could determine prior to pregnancy whether or not they actually carry the allele and, consequently, whether amniocentesis might be necessary. Analogously, individuals potentially at risk for heritable disorders, including some forms of cancer, of which expression occurs late in life, ought to be able to determine in advance of obvious symptoms whether they are at risk for the disease. Moreover, when a specific linkage is found, further refinements should be able to increase the available polymorphism and tighten the linkage until a valid tool for preventive medicine is established.

A large set of RFLPs will have many other uses in human population genetics. A large set of truly neutral markers will reopen questions of genetic distance between geographical isolates and may shed more light on population structure and selection as competing mechanisms of allelic variation and linkage disequilibrium. Multilocus theory will have abundant data to test its predictions.

Human cytogenetic analysis will also benefit from this new technology. Often birth defects phenotypically resemble known chromosomal deletions but show no missing bands on the suspect chromosome. With a map of RFLPs, one could look for areas where the alleles of one parent were entirely missing and infer a deletion too small to be detected by standard techniques. Similarly, trisomies would produce unique patterns which could reveal small translocations.

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Mr. **Gore**. Very provocative testimony. I will come back with some questions.

Dr. Theodore Freidmann is a professor of pediatrics at the University of California School of Medicine in San Diego at La Jolla and I would like to welcome you and invite you to proceed.

Mr. **Friedmann**. Thank you, Mr. Chairman.

Before I forget, I would like immediately to support what Dr. Skolnick has just said about what seem to be complex and multigenic traits. What we consider very complex and multigenic today is likely to turn out to be rather simple tomorrow when we finally come to understand it. I can't give you specific examples of that, but the techniques that we consider today to be commonplace, the characterization and dissection of the human gene, the isolation and sequencing of genes were cell techniques really quite beyond our wildest imagination just 10 or 15 years ago. We are using these techniques every day now. So I think that we have a problem being able to predict exactly how complex some genetic defects are going to be.

In order to anticipate and understand the possible future roles for genetic manipulation in the treatment of human disease in general, and I will try not to be too specific, it is helpful to understand our current views of genetic diseases, how they are treated today, and to ask if there is a need for different kinds of therapy such as gene therapy, precisely what its goals might be and then whether this sort of treatment is possible now or will become possible in the future.

I will try not to reiterate what has been discussed so far by previous speakers.

The first objective is to ask what we understand by the term genetic disease. I think that is one aspect of this developing field that is changing extremely rapidly.

Since the beginning of the 20th century when Sir Archibald Garrod and others rediscovered Mendel and established the notion of inborn errors of metabolism, we have often felt that genetic disorders were rather rare and obscure and affected only a few of us. Until very recently we have continued under that concept of genetic disease—that it does not affect the bulk of the population, even though disorders such as cystic fibrosis and sickle cell anemia have large populations at risk. We have had the impression that most of us were not affected by genetic disorders.

I think that during the last 10 years that concept has completely turned around. It is now quite clear that we are beginning to recognize that there are very major genetic components, genetic determinants to some of the most important and burdensome diseases that our society endures, including diseases such as cancer, cardiovascular disease, diabetes, schizophrenia, disease which, at first glance are not obviously genetic but which we now understand to constitute a complex class of disorders that result from interactions of environmental and genetic factors. As we come more and more to understand them, we are coming to recognize that there probably are genes that we may be able to isolate and study which have very important effects on our health in these various diseases.

Some of the most recent and most exciting developments, I think, in this field are coming from the isolation and characterization of human oncogenes. These genes are normal parts of the human genetic apparatus that normally may play some important part in differentiation and development of the human organism, but under conditions where those genes are either mutated, rearranged, moved to different parts of the chromosomes or expressed either at the wrong time or in improper amounts, those genes seem to be causally, or at least very intimately, related to the development of most and perhaps even all human cancers.

So I think one has to consider cancer a genetic disease. Similarly, the relationship that Dr. Skolnick described already between the HLA genes or other kinds of genes with autoimmune diseases, to resistance to infection or to other environmental poisons and toxins makes it clear that some human disease results from defects in these genes, and that such defects are expressed through an interaction of genes and environmental factors. Some of the so-called autoimmune disease, in which the body mistakenly recognizes something within itself to be foreign and tries to reject it, including forms of arthritis, multiple sclerosis and many other diseases, are correlated with the presence of specific HLA genes. Those diseases can therefore quite properly be considered to be genetic diseases.

I'm also quite convinced that genetic factors will be found at the heart of many other degenerative diseases. Even the so-called normal aging process, mental disorders such as schizophrenia, and many other presently mysterious diseases will eventually be recognized to result at least partly from genetic defects.

So all these kinds of major public health burdens that our society has, I think, should be considered in a discussion of genetic disease. We don't have the luxury, any longer, of considering genetic diseases to be rather rare curiosities, as we might have done just a few short years ago.

The next question is, if genetic disorders are as common as all that, how are we doing at the moment in treating most of them? I think, again, until recently we have had the luxury of feeling that we are doing fairly well. It is certainly true that some disorders such as PKU, galactosemia and several others are well-treated by dietary restriction, drug therapy and vitamin therapy and other manipulations.

But, on the other hand, I think it is now every clear that we are doing, in fact, very badly with the treatment of most genetic disorders. Even the majority of the rather straightforward and classical enzyme defects that fill the compendium which Victor McKusick has compiled of all human genetic diseases are either unapproachable or at best only partially ameliorated by the standard or traditional kinds of therapy that we have available today.

Because of these factors, I think there is little justification for a great deal of optimism about our ability to use, or improve upon traditional kinds of therapy for the bulk of these diseases. We must of course continue doing what we are doing, to improve the tools we have, the methods that are partially effective, to press ahead with more traditional pharmacological approaches, looking for new drugs, looking for new procedures. Without any doubt, new and effective management of some disorders will result from improvements in our present approaches.

A further major improvement of therapy of genetic disease will come when the immunological problems of tissue and organ transplantation are solved. Major steps in that direction are now being taken, and one can expect major improvements in the not too distant future. That means that organs damaged by genetic defects, including the bone marrow and most other organs, may eventually be relatively easily replaced. Tissue transplantation will take its place in therapy, but clearly that is not going to come very quickly. In fact, it is the view of some that the progress in that field is now being overshadowed and overtaken by the progress in molecular genetics and in our ability to manipulate genes.

The standard approach that we have had to treating genetic disease can be traced to our general view of inborn errors of metabolism as pictured by Garrod, and if one thinks about it for a moment, it is clear that all approaches to all human genetic disease until now have been aimed at a site distant from the site of the defect. There has been no capability until now even to imagine treating a disorder at the site of the genetic defect. We have always been content with treating symptoms, replacing missing enzymes, replacing missing products. In some cases, those treatments do work. But as I have tried to demonstrate earlier, our failure effectively to treat the bulk of human genetic diseases may be related to the fact that we are simply aiming at the wrong link in the chain of pathogenesis of disease. For some disorders one may begin to think about aiming at the site of the genetic defect rather than the site of the metabolic derangement.

I won't reiterate the kinds of models that have been developed for gene therapy. Ideally, as Dr. Axel said, one would like to put a gene into its normal site in the genome and place it under its normal and accustomed cellular regulation so that one does not damage the cell any further. That technique is not yet available in high animals, although it is now apparently successful in fruit flies and lower animals. Sooner or later, though, such site-specific gene replacement is likely to become possible, and I think it will be possible eventually to delete the defective gene and insert the normal copy.

The question of genetic modification of germ or somatic cells, I think, has been adequately covered. I think one cannot simply dismiss the idea of modification of germ cells in some instances of genetic diseases. There may at times be convincing medical and genetic arguments in favor of germ cell modification, even though such a capability does pose more troublesome ethical and moral questions, I think, than somatic genetic manipulations. At the moment, however, I don't think that it is easy to dismiss such a manipulation, but it is not the model that most people are considering.

The question of whether science is ready yet with gene therapy is an important question. The committee is probably aware of the meeting held at the Banbury Center at Cold Spring Harbor in February of this year, a meeting designed specifically to ask whether these techniques are ready yet and whether they will be in the near future. Much of what I say, at least part of what I say, is not only my own viewpoint, but a description of an informal consensus from the meeting. That consensus I think, is that we are not yet ready for major kinds of genetic onslaughts on the human genome in an attempt to carry out gene therapy. But I do think most people at the meeting would agree with the contention that there is probably a need to think about unusual or new forms of therapy, including gene therapy. Currently available therapies are not effective and one should consider genetic approaches to disease management together with other approaches to disease therapy.

There is one aspect to the discussions that has not yet been raised and which came up at the Banbury Center meeting. That is the idea that medicine does not always have the luxury of holding back and waiting for optimum knowledge before it presses ahead with an experimental or controversial new therapy. I think that this is the basis, in fact, for some of the supporting arguments that were advanced for the experiments by Dr. Cline. I think there is perhaps something compelling about the argument that medicine historically has not been willing to defer indefinitely on difficult or dangerous new paths until knowledge might become optimum. In fact, medicine historically has often used partial, imperfect or incomplete knowledge to press ahead with new attacks on disease. It always has done so, I think, and will continue to do so. The dilemma that we face is that of knowing how to balance that perceived moral obligation to proceed with imperfect knowledge for the sake of battling human suffering against the scientific dangers and the moral and ethical reservations that some of us feel about aspects of this kind of work.

The development of some forms of genetic therapy is a logical and consistent development. There is probably a need for it. There is certainly a need to fill major gaps in our currently ineffective modes of treatment for most diseases. Genetic manipulation will eventually take a place in the treatment of certainly not all, and perhaps not even most, but certainly some disorders that will not be otherwise approachable by other techniques.

Thank you.

[The prepared statement of Theodore Friedmann follows:]

Theodore Friedmann, M.D.

In order to anticipate and understand the possible future roles for genetic manipulation and treatment of human disease, in other words human gene therapy, it is helpful to understand our current views of genetic disease and how they are treated, to ask if there is a need for gene therapy and precisely what its goals might be, to determine whether in fact it is possible now or will be come possible in the future, and to identify potential risks and problems that we might envision.

Medicine now recognizes something like 3 or 4 thousand human genetic diseases, ranging all the way from very obscure and rare disorders to common and major health problems such as sickle cell amemia and cystic fibrosis. We are also coming to recognize the very important genetic factors in a large number of other disorders that are major health burdens in our society, including cardiovascular diseases leading to strokes and heart attacks, forms of schizophrenia and other mental disorders, diabetes, neurological diseaseds such as Huntington's chorea and multiple sclerosis, and even aspects of the so-called normal ageing process. As this Committee has already heard, we now have methods available that, in principle, enable us to isolate and characterize many of the genes responsible for these disorders. Some of the most exciting and important studies in this direction have recently suggested that most or perhaps all human cancers are accompanied by rearrangements of a variety of normal sequences in our DNA, the so-called oncogenes, several pf which have already been isolated and which promise to tell us a great deal about the origin and the development of many human cancers.

The point of all this is that we are now coming to understand that some of our society's major killing and crippling diseases such as cancer, degenerative, infectious, cardiovascular, neurological and other diseases are accompanied by changes in the arrangement or expression of genes, and therefore should be considered genetic diseases.

But even if our concept of genetic diseases has broadened a great deal, do we really think that we need new kinds of therapy? Don't we already have adequate treatments now for most of these diseases? The obvious answer to that question is, "No". For each successful treatment of a human genetic disease, as in the case of some forms of hormone deficiencies, PKU and other diseases, there are many more disorders for which treatment is, at best, only partially effective and, in many more instances, completely ineffective.

If current therapy is inadequate, what more do se need to improve treatment of genetic diseases? Obviously, major advances will continue to be made in the development of improved and new forms of traditional and symptomatic treatment, in the discovery and development of new drugs and techniques. Major problems that we now have with the consequences of tissue transplantation will be overcome, thereby making tissue and organ replacement simpler and more effective as a means of therapy for some diseases. But for many other genetic disorders, these developments will continue to be ineffective or will be overtaken and surpassed by methods that take advantage of our ability to make specific and directed changes in the abnormal gene.

One of the most impressive features of medical therapy for genetic diseases has until now been the fact that treatment has necessarily always been aimed at a step distant from the defect itself, as illustrated in Fig. 1. Mutant or incorrectly organized genes lead to the production of defective enzymes, to abnormal metabolic pathways and to cell or tissue damage. In developing treatments we have classically tried to replace or enhance the activity of defective enyzmes (4,5,6) prevent or treat the accumulation of toxic materials (7,8), to replace missing products such as insulin and other hormones (9) or to treat the symptoms of genetic disease (10,11). We have never been able to treat any diseases at the level of the mutant gene itself. This is what may soon become possible as a result of studies in molecular human genetics; in other words gene therapy.

By gene therapy, we have come to imagine treatments in which normal forms of genes are inserted into patients in such a way as to introduce a missing or abnormal funvction. This Committee has heard of the enormous progress recently made in isolating and characterizing genes and in developing viral vectors and other methods of re-inserting functional and expressed genes into single cells and, in fact, into whole animals. This rapid progress will continue, and we will without much doubt soon be able to insert new hormone, enzyme or other functions into the somatic, or non-reproductive cells of a whole animal in a way that allows proper and controlled expression of such new genes. Ideally, one might want to remove the defective gene and replace it with a normal copy, and while that technique has not yet been developed, I suspect it will be in the not too distant future.

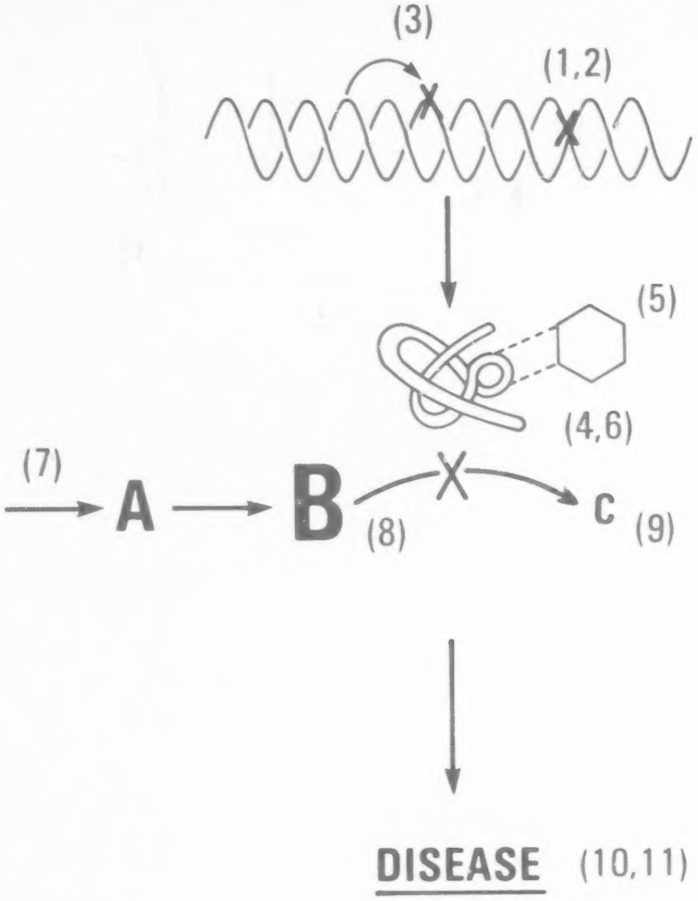
Theodore Friedmann, M.D.

The insertion of functional genes into the somatic cells of whole animals seems not to be an unsurmountable problem, and I suggest that some, certainly not all and probably not even most, forms of human genetic disease will eventually be managed and treated most easily and efficiently by a manipulation of the defective gene in a given patient. Diseases resulting from defects in the immune system, such as several enzyme deficiency immunological disorders, and disorders of hemoglobin production, as in the thalassemias, seems to be the disease models most likely to be approached by gene insertion into somatic cells.

Do we imagine that it might be useful deliberately to insert genes not only into the somatic cells but also into the reproductive cells of patients in order to correct an anticipated gene defect in future generations? It certainly seems to me to be possible that that kind of genetic change will eventually become feasible technically, and it is even possible to imagine kinds of human genetic disease in which it might be useful. For instance, in the management of Huntington's chorea and other similar dominant diseases, the development of methods for genetic correction in a patient might profitably be extended to the patient's reproductive cells and therefore to future offspring, half of whom would otherwise be destined to develop such a disease.

Are we ready yet to use genetic manipulation for the treatment of any human diseases? I think it's true that the consensus among most human geneticists at the moment is that we still have more to learn about the fate and expression of transplanted genes before we undertake studies with human beings.

Many, but again not all, of those people will also agree, however, that there probably are indications and real needs for treatment of human diseases at the level of defective genes, and that such treatments will and quite properly should come in the not too distant future. While we should recognize that there is something special and possibly unique about Medicine and its need to use even imperfect knowledge in order to relieve suffering of patients with disease, the development of methods of gene therapy should result from rigorous and careful scientific studies in order to ensure the safety of patients and research subjects. In my view, the development of methods for genetic treatment for human disease is logically consisent, inevitable, and necessary to fill major gaps in the effectiveness of currently available therapies. We may not be ready quite yet, but I think that we must work toward the goal of understanding genetic diseases well enough so that genetic manipulation will become possible for some diseases. Out of such knowledge will come not only this conceptually new kind of therapy but certainly also many improvements in more traditional forms of treatment.



MUTATION, ORGANIZATION DEFECTS

1 GENE REPLACEMENT
2 INDUCTION, REARRANGEMENT
3 DRUGS

DEFECTIVE GENE PRODUCT

4 ENZYME THERAPY
5 CO-FACTOR THERAPY
6 TISSUE TRANSPLANTATION

METABOLIC ERROR

7 DIETARY RESTRICTION
8 DRUG THERAPY
9 PRODUCT REPLACEMENT

ORGAN DAMAGE

10 SYMPTOMATIC THERAPY
11 ORGAN TRANSPLANTATION

Our final witness today is Dr. French Anderson who is Chief of the Laboratory of Molecular Hematology at the National Institutes of Health. Welcome and please proceed.

Dr. ANDERSON. Thank you, Mr. Chairman. I appreciate the opportunity to testify today.

My name is Dr. W. French Anderson. As a physician, I have been actively engaged in research in the field of molecular biology for over 20 years. My specific area of interest is gene therapy for lethal genetic anemias—specifically, Cooley's anemia and sickle cell anemia. In addition, I have written and spoken on the ethical implications of gene therapy over the past 10 years. Presently, I am Chief of the Laboratory of Molecular Hematology at the National Heart, Lung, and Blood Institute, one of the Institutes of the National Institutes of Health. I am pleased to be here as a scientist to testify on the scientific and ethical aspects of genetic engineering as applied to clinical medicine.

Previous speakers have covered the scientific state-of-the-art of genetic engineering and the need for gene therapy. As the final panelist of the day, I would like to discuss the possibilities for therapeutic application of genetic engineering for human beings. I will describe four levels of possible future application. Each in turn is more difficult, will require greater technical expertise and knowledge, and has additional ethical considerations. Although predictions are always risky, I will suggest the timeframe around which we might expect to see the technical capability for carrying out each level, and I will give my own views on the ethical implications of each level. In addition, I will suggest the further knowledge which I believe is still necessary before any attempts at gene therapy in human beings should be undertaken.

The four potential levels of the application of genetic engineering for human beings are—and I should say as an aside that this is in close agreement with the previous panel:

First, gene therapy of somatic—body—cells: this would result in correcting a genetic defect in a patient.

Second, gene therapy of germ line—reproductive—cells: this would require the insertion of the gene into the reproductive tissue of the patient so that the defect in his or her offspring would also be corrected.

Third, "enhancement" genetic engineering: by this I mean the insertion of a gene to "enhance" or alter a known characteristic—for example, hair color.

Fourth, "eugenic" genetic engineering: this would mean attempts to alter or improve those human traits each one of which is coded by many genes for example, personality, intelligence, character, formation of body organs and so on.

Let us examine each of these four levels in more detail:

First, somatic gene therapy. There are many examples of known genes which, when defective, produce serious or lethal disease in the patient. An example is beta thalassemia, otherwise known as Cooley's anemia. This is a lethal genetic anemia in which an infant is unable to make normal hemoglobin the oxygen-carrying pigment of the blood. Without blood transfusions the infant may die as early as a few months of age. The present state-of-the-art of genetic engineering allows us to obtain a normal hemoglobin gene from the tissues of a normal individual and to transfer this gene into some or all of the cells of an experimental animal most commonly, the mouse. It is not yet possible to get the normal gene to go specifically to the correct cells within the animal, namely, the red blood cells, or to assure that the gene will function appropriately and produce hemoglobin within the animal's body.

However, information obtained from studies in animals is accumulating rapidly on a number of fronts, and as a result, I believe that within the next one to two years a genetic disease in a laboratory animal will be at least partially corrected by gene therapy.

The present techniques being used in attempts to treat mice, however, may not be applicable to humans. Approaches that would be suitable for children and adults must be developed before gene therapy should be attempted in patients. Efforts are underway, for example, to use virus-like molecules for this purpose. Specifically, the desired gene with its regulatory sequences would be covered by a "coat" just as occurs in many viruses. The coat would recognize, and get itself and the DNA it carries into, a specific cell type: bone marrow cells for hemoglobin genes, liver cells for liver genes, et cetra. This approach will take time to develop. Other possiblities are also being explored. It will probably be 5 to 10 years from now before a gene therapy experiment in humans could be conducted with some reasonable expectation of success. The latter stipulation, a reasonable expectation of success, is necessary to make the experiment sensible from a medical point of view and ethical from a social point of view.

What knowledge is necessary in order to provide a reasonable expectation of success? Two years ago, John Fletcher and I suggested three criteria that should be satisfied in animal studies before gene therapy in human beings should be attempted. These three requirements appear to have received widespread support among physicians, scientists, and ethicists. They are as follows. It should be shown in animal studies that the gene to be used in a human therapeutic attempt:

First, can be inserted into the correct target cells and will remain there for a reasonable period of time;

Second, will function sufficiently well to be effective; and,

Third, will not cause serious harm to the animal.

These critera are very similar to those required prior to the use of any new drug, therapeutic procedure, or surgical operation. The criteria simply state that the new treatment must get to the area of disease, correct it, and do more good than harm. Some flexiblity is necessary since the criteria might be altered for a critically ill patient for whom no further conventional therapy is available. The exact definition of what is a "reasonable period of time," what is meant by "sufficiently well", how effective is "effective," how serious is "serious," are questions for ongoing discussion as more and more is learned about gene therapy. Ultimately, an institutional review Board must decide if a given protocol is ready for human application. I believe, however, that once the criteria are satisfied that is, when the probable benefits for the patient are expected to exceed the possible risks, then attempts to cure human genetic disease by treatment with gene therapy would be ethical. The goal of biomedical research is, and has always been, to alleviate human suffering. I believe that gene therapy is a proper and logical part of that effort.

The second level of genetic engineering, gene therapy of germ line cells, may not be too different, in a technical sense, from the first. It requires inserting the gene not only into the appropriate cells of the patient's body, but also introducing it into the germ line of the patient in such a way that it will be transmitted to offspring and will be functional in the correct way in the correct cells in the offspring. Based on the small amount of information now available from animal studies, the step from correction of a somatic cell defect to correction of the germ line may not be too difficult. Germ line transmission of inserted genes in mice has been obtained by a number of laboratories.

But even though the technical capability may be present to attempt germ line therapy in humans soon after somatic gene therapy, there are major additional medical and ethical concerns to consider. These concerns center primarily around the question: Will the transmitted gene itself, or any side effects caused by its presence, in some manner adversely affect the immediate offspring or their descendants? Since in this case, one must study several generations of progeny to obtain answers, it will clearly take longer to gain knowledge on the long term safety of germ line gene therapy than on somatic gene therapy. It is this area which most needs careful ethical consideration well in advance of the time when the technical capability for carrying it out arrives. The public should be fully aware of all aspects of this issue and take an active part in the ongoing discussions. My own feeling is that, since this is still the correction of a genetic defect—in this case, one that would have occurred in the offspring—the procedure, after thorough testing in animals, would be ethical and appropriate.

The third level of genetic engineering, which I call enhancement genetic engineering, is considerably different from the first two. This is no longer therapy. Now we are discussing alteration for its own sake; namely, the insertion of a single gene or a small number of genes, which codes for a product (or products) the effect of which is some characteristic that the individual wants: for example, a different hair color. There is a major additional scientific hurdle to cross, which I will discuss in a moment as well as serious new ethical issues to consider. I am personally opposed to the use of genetic engineering for enhancement purposes, but I can see where reasonable persons could differ on this issue. It should be an interesting area for discussion tomorrow. As an aside let me add that in discussing the line that one could draw, I would draw the line at this point.

The scientific hurdle to overcome is a formidable one. Up to now, we have discussed the correction of a defect, of a "broken part," if you will. Fix the broken part and the human machine should be functional again. Replacing a faulty part is different from trying to add something to a normally functioning system. To insert a gene in hopes of improving or selectively altering a characteristic might endanger the overall metabolic balance of the individual cells as well as of the entire body. Medicine is a very inexact science. Every year new hormones, new regulators, new pathways are discovered. There are clearly many more to be discovered. Most impressive is the enormously intricate way that each cell coordinates within itself all of its thousands of pathways. Likewise, the body as a whole carefully monitors and balances a multitude of physiological systems. It will take a great deal of additional research to understand what the effects will be of altering one or more major pathways in a cell. To correct a faulty gene is probably not going to be dangerous; but intentionally to insert a gene to make more of one product might adversely affect a dozen other pathways.

It seems to me, therefore, that it will take a long time to acquire sufficient information to understand the effects of arbitrary attempts at alterations of the genetic machinery of a human. One can already influence almost any characteristic one wishes by the use of drugs, cosmetics, plastic surgery, etc. Would it be wise, safe, or ethical for parents to give, for example, growth hormone (now that it is becoming available in large amounts to their normal sons in order to produce very large football or basketball players? Obviously, this is a disturbing thought. But why would anyone (even if they could) want to insert a growth hormone gene into their normal child? Once it is in, there is no way to get it back out. Reflexes, coordination, balance: all might be grossly affected. In addition, even more serious questions could be asked: might one alter the regulatory pathways of the cell, inadvertently affecting cell division or other properties? In short, I believe that we know too little about the human body to chance inserting a gene designed for "improvement"—whatever that means—into a normal healthy person.

The fourth level is that of "eugenic" genetic engineering. This area has received considerable attention in the popular press, with the result that at times unjustified fears have been produced because of claims that scientists might soon be able to re-make human beings. In fact, however, such traits as personality, character, formation of body organs, fertility, intelligence, physical, mental, and emotional charateristics, etc., are enormously complex. Dozens, maybe hundreds, of unknown genes which interact in totally unknown ways probably contribute to each such trait. Environmental influences interact with these genetic backgrounds in poorly understood ways. It may never be possible to influence in a predictable manner any of these traits; at a minimum, it will be many decades. Therefore, there is no purpose to a scientific discussion of eugenic genetic engineering; there is simply no science to discuss. But from a philosophical standpoint, a discussion of the ethics of eugenic genetic engineering is very important. After all, what is it that makes us human? Why are we what we are? Are there genes which are indeed "human" genes? If we were to alter one of these genes would we be less than human? These are important questions for us to think about and discuss from a theoretical and philosophical point of view. These discussions will occur tomorrow and I look forward to them. Let me say now, however, that if eugenic genetic engineering were possible today, I would be strongly opposed to it on philosophical and ethical grounds.

In summary, I suggest that gene therapy for human genetic disease should be possible in the near future; the scientific basis on which this new therapeutic approach is founded can be analyzed at the present time in a concrete practical way. The ethical justification for its use can and should be delineated and made available to the public for their thought and consideration. Enhancement genetic engineering should be possible in the not too distant future and, therefore, its medical and ethical implications also need continuing discussion. But eugenic genetic engineering is purely theoretical and is, from a practical standpoint, impossible for the present; the topic is valuable for reflective thinking but not for scientific discussion.

One final statement: I feel very strongly that the use of gene therapy, at the approriate times and under the proper safeguards, is ethical and proper. Many of the fears generated by some articles in the popular press are simply unfounded. Insertion of single functional genes may soon become possible, but claims that new organs, new personalities, master races, or Frankenstein monsters will be created have no place in present-day reality. Even so, we are all concerned about the possibility that genetic engineering might be misused in the future. I believe that the best insurance against potential abuse is a well-informed public. Gene therapy has the potential for tremendous good by reducing the suffering and death caused by genetic disease. We can all look forward to the day when this powerful new therapeutic procedure is available.

[The prepared statement of French Anderson follows:]

Mr. Chairman and Members of the Subcommittee: I appreciate the opportunity to testify today. My name is Dr. W. French Anderson. As a physician, I have been actively engaged in research in the field of molecular biology for over twenty years. My specific area of interest is gene therapy for lethal genetic anemias (specifically, Cooley's anemia and sickle cell anemia). In addition, I have written and spoken on the ethical implications of gene therapy over the past ten years. Presently, I am chief of the Laboratory of Molecular Hematology at the National Heart, Lung, and Blood Institute, one of the National Institutes of Health. I am pleased to be here as a scientist to testify on the scientific and ethical aspects of genetic engineering as applied to clinical medicine.

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Mr. GORE. Thank you very much. And thanks to all of the members of this panel. I have a few questions.

First of all, Dr. Kan, what diseases other than sickle-cell anemia and beta thalassemia can we now screen through genetic techniques?

Dr. KAN. You mean using the recombinant DNA technique?

Mr. GORE. Yes.

Dr. KAN. I think at the present time, sickle-cell anemia and thalassemia are the two that have been performed most often. But there has been some new development. For example, I mentioned in my testimony that a part of DNA close to one type of muscular distrophy has been isolated and it may be possible in the very near future to use this type of technique for muscular distrophy.

There is also another type of development which has emerged from the laboratory, that is a new technique to look at a single nucleotide change. In the case of sickle-cell anemia, we can detect a single change in one base because there happens to be a restriction enzyme that recognizes that site. But there are a lot of other changes in the DNA which do not occur at a site of restriction enzyme recognition.

Dr. Bruce Wallace, Dr. Salvio Woo, and their collaborators have now devised a method of specifically looking at that one base change which causes the genetic defect. I heard recently this has been applied to a disease due to a deficiency of an enzyme called alpha-1 anti-trypsin. Because the gene for alpha-1 anti-trypsin has been cloned, therefore they can use this type of technique.

Mr. GORE. All right. Thank you very much.

Dr. Skolnick, when you do your genetic mapping, what kind of tools do you use?

Dr. SKOLNICK. We use individuals who are studied in a clinic.

Mr. GORE. No; I am talking about the instruments.

Dr. SKOLNICK. Computers and simple laboratory apparatus.

Mr. GORE. Microscopes?

Dr. SKOLNICK. No; it is an electrophenic gel box. It is very similar to what was described by Dr. Kan.

Mr. GORE. Now, with the help of the computer, you are able to scan lots of information at once?

Dr. SKOLNICK. The computer tells us when two genes are traveling together as neighbors or not.

Mr. GORE. I see. And it can tell you that, it can cover a great deal of information quickly and tell you where two genes are occurring together?

Dr. SKOLNICK. Yes.

Mr. GORE. So in terms of the analogy used by the last panel, if you were looking at a strand that went from here to Baltimore and back, a computer could do that pretty quickly?

Dr. SKOLNICK. Really the problem is generating that information with the gel boxes, with the electrophoresis. The computer part is not a problem. The computer analysis is relatively small compared with the amount of laboratory work required.

Mr. GORE. How sophisticated is genetic mapping likely to become? You have described a technique that is useful in correlating patterns within a family group. You have said in response to an earlier question that there are some examples of unrelated individuals having a similar pattern. Is it likely that we will develop a computerized library of data on the human genome and all the variations?

Dr. SKOLNICK. There already is, at Yale University, a computerized gene map that has compiled all of the information and all of the references of known mapped genes. There are gene mapping workshops every 2 years to update that information and pass it through a panel that decides this can go on the map, this cannot go on the map; so that we all agree on where things are, what sufficient scientific knowledge is, and so on.

Mr. GORE. Someone told me that the amount of data on that map was doubling, some fantastic doubling time.

Dr. SKOLNICK. Perhaps once every year, 2 years.

Mr. GORE. Every 6 months was the figure given to me.

Dr. SKOLNICK. I could not debate the exact speed. It is very rapid, I would agree.

Mr. GORE. If the information about the human genome contained on the computerized map doubles every year, then presumably it won't be that long before you have a pretty comprehensive map.

Dr. SKOLNICK. That's right. There were 25 classical genetic markers that were useful before the recombinant DNA markers came along. As of June 1981 there were 25 new markers, recombinant DNA markers. Now 1 year later, there are 50 more; that is 100 markers. So the number of genetic markers is certainly doubling every year, and we have calculated that it will require 400 markers until we have found enough markers to cover the whole gene map with sufficient street signs so that you don't get lost.

Mr. GORE. Well, ——

Dr. SKOLNICK. That is approximately 2 years from now. Very immediate.

Mr. GORE. So 2 years from now you will have street markers——

Dr. SKOLNICK. Along the whole gene map.

Mr. GORE. Along the entire gene map. So you will be able to tell what county or what block—I'm torturing these metaphors mercilessly—you will be able to tell roughly what part of the map a particular gene is in.

Dr. SKOLNICK. Right.

Mr. GORE. Isn't it reasonable to assume once you get those street markers, 400 of them, then the resolution of your focus will change, and you will begin to fill in the gaps between the street markers?

Dr. SKOLNICK. Absolutely. Once you have mapped a gene, to continue the metaphor, to a county, you can then look for more markers just within that county, and you try to get markers every mile, and then every block and get closer and closer.

Now the size of the genome is so large, it is not a practical tool for actually isolating a gene, for actually getting so close that you can pick it out. But you can get close enough so that you would be able to diagnose with say 99 percent certainty whether someone did or did not have a disease.

Mr. GORE. When do you think you will get down to the voting precincts?

Dr. SKOLNICK. They are coming.

Mr. GORE. When you say the genome is so large, give me an appreciation.

Dr. SKOLNICK. Three billion bases, as was said earlier. Three billion letters in the A-C-T-G code. And the genes appear to be spaced every 5,000 or 10,000 bases. And there is a technique which hasn't been mentioned yet called walking, using recombinant DNA's, if you start at one point of the genome, you can take an overlapping recombinant DNA insert and walk another 10,000 bases, then another 10,000 and another 10,000 bases.

So once you get a part of a gene you can walk around it to describe its vicinity. It is exciting, isn't it?

Mr. GORE. Well, it is alternately exciting and terrifying.

Dr. SKOLNICK. Right.

Mr. GORE. You said that insurance companies currently don't use this technique. Let's suppose they did and found that they could predict longevity. Not an unreasonable assumption, is it?

Dr. SKOLNICK. There are two problems. One is that insurance companies might decide to start using genetic knowledge to decide who is insurable or not, and that would create a problem. What I was referring to is that they are willing to pay for bills, once a person is diseased, but not willing to pay, say, half that amount of money to screen the family and find two or three people and save themselves—say spend $10,000 to save $60,000.

Mr. GORE. I understand. And I think your approach is extremely useful, in pointing out that our society is not only unprepared for the magnitude of the implications of this new technology, the bioethical questions that are presented—we tend to think of those in terms of avoiding some of those bad scenarios that people discussed.

But neither are we prepared for the potential good and how to exploit the potential good, as for example your mention of the need to anticipate and create an entirely new medical care delivery system, an entirely new system focused on preventative medicine and the use of these techniques.

We have had several hearings on the technology of genetic screening, and we have looked at it in employment settings. We focused on site genetic screening, and also looking at HLA antigens. But this technology you are describing has enormous implications for that subject as well, does it not?

Dr. SKOLNICK. Absolutely. For one example, if 200 million Americans were screened for hemochromatosis at a cost of $5 or $10 each, or perhaps at that level, $2 each; we would avoid 1 million causes of death. They would eventually die of something else. But we would have removed that one cause of death from 1 million individuals.

Mr. **Gore**. OK.

Dr. Friedmann, you agreed with Dr. Skolnick that it is probably too glib to dismiss the possibility of directing genetic engineering for specific complicated traits, like mental skills, because things we now think of as multigenetic, having many genes participating in it, may be found to have a very simple lever or crucible that will determine the rest of the complex. Is that correct?

Dr. **Friedmann**. Yes, I think that is true. Obviously, most of them will continue to be intractible, and too difficult to deal with. I don't know which are the ones that are going to appear to be very simple on the basis of the isolation of a specific gene. I can give you just one of our current and most favored examples, and that is the Lesch-Nyhan disease.

This is a disease, a very rare one, a disorder that is inherited like hemophilia since the site of the defect is on the X chromosome. Affected children are retarded, have cerebral palsy, and have a very peculiar kind of self-mutilation behavior in which they bite their fingers and their lips—not their fingernails, but their fingers. They simply bite the tips of the fingers off.

Some people like to think of this as a peculiar kind of aggressive behavioral aberration, and the evidence is that that is a result of a single base change in one single enzyme. I think it is certainly not a clean analogy, but it does say that very complicated kinds of behavior patterns in fact have very simple genetic bases.

Mr. **Gore**. Yes.

Dr. Anderson, help me appreciate more fully your distinction between enhancement and your fourth category which you describe as eugenic.

Dr. **Anderson**. First let me say that I think that there is a remarkable degree of agreement among everyone who has testified today. I have not heard anything that, within the context that the speaker was making the statement, I would disagree with.

There are times when it sounds like there are disagreements, but within the context that the person was speaking, there is really no disagreement among any of us, which I think for any topic as emotional as this one is very extraordinary.

Mr. **Gore**. I agree.

Dr. **Anderson**. The areas of enhancement and eugenic genetic engineering will fuse into each other, By enhancement genetic engineering I mean the attempt to alter those properties which are controlled by one or two or three genes. Here we can possibly make a very specific modification by inserting a known gene.

Eugenic genetic engineering includes all those traits about which we are now ignorant: personality, character, et cetera. As Dr. Friedmann pointed out, as we gain more knowledge, areas that might now be called subjects for eugenic genetic engineering might move into the enhancement category. But the timeframe for this might be very long. To blindly give a human being a gene that one thinks might influence personality, for example, would be to use a human being as a guinea pig. And that is what I disagree with.

Mr. **Gore**. You are familiar, of course, with the experiments by Dr. Cline?

Dr. ANDERSON. Yes, sir.

Mr. GORE. What is your opinion of that effort?

Dr. ANDERSON. I would agree with what was said by the previous panelists, and that is that the experiment was premature then, it would be premature now, and it will be premature for at least the next 2, 3 or 4 years.

Mr. GORE. Because not enough is known as a result of animal experience, and therefore a calculation of the risk benefit, the ratio, is impossible.

Dr. ANDERSON. Right, exactly. If you go through the three criteria that Dr. Fletcher and I have listed, first you have to be able to get the gene into the proper cells, and that one Dr. Cline was able to do in part, namely, he could take out a small portion of bone marrow and get the gene into a few of those cells.

The difficulty is that he could only influence a tiny fraction of all of the cells in the bone marrow. So even if the experiment had worked in every other way, it would have been impossible to have ever detected a positive result.

The second thing is getting the gene to function efficiently. It is still not possible to get a human gene to function efficiently.

Mr. GORE. Well, if you have a patient who is going to die unless you come up with some treatment that is as yet unknown, shouldn't that affect the cost benefit, or the risk benefit?

Dr. ANDERSON. Absoutely. In a critically ill patient who has no possibility for help by conventional therapy, it is worthwhile to try experimental procedures. But not as a shot in the dark. I simply don't believe that human beings should ever be used to test a shot in the dark. That if there is no evidence that that gene is going to work in an animal model, then there is no reason, no medical reason to use it.

Mr. GORE. Does anyone else on the panel disagree with the basic view expressed by Dr. Anderson there?

Dr. FRIEDMANN. Maybe I could just amplify a bit. Maybe I am really getting into trouble when I comment on this subject, since I really don't know what I think on that issue.

One might justifiably say that scientifically the experiments were premature and perhaps even that they still are premature. On the other hand, I think there are other factors to weigh. The scientific factors are not alone in the calculation of the worthiness of these experiments, although they are of prime importance. There are the possible obligations, as I tried to say in my testimony earlier, that Cline and other people in that same sort of position may have recognized, obligations strong enough to override the prematurity of the science.

I think medicine often goes to rather extreme lengths in the face of terminal or untreatable illness to use untried and improven new tools. I think much of what we come to recognize today as very effective therapy for cancer began, and even now continues to develop as a result of these very unlikely shots in the dark. I am not at all convinced that medicine is or can be held to the same standards as less applied science. Ideally, it would be expected to be no less rigorous, and perhaps even more rigorous since human lives and welfare hang in the balance. I think that it is difficult to know when to accept what little knowledge is available and accept the risks of the early applications of imperfect knowledge to problems of human health. One doesn't always know when to accept one's ignorance or imperfect knowledge and proceed.

Mr. **Gore**. Are you familiar with an experiment attempted in 1970 on three German girls by Dr. Stanfield Rogers?

Dr. **Friedmann**. The arginase treatment?

Mr. **Gore**. Yes. How would you contrast or compare that with Dr. Cline's experiments?

Dr. **Friedmann**. I think that when those experiments were done, there was so little molecular and biochemical understanding of that process that I think those experiments really had little foundation in science.

In fact, the presumption was that Shope virus carried into a cell its own information for the new enzyme, arginase, missing from the cells of the patients. In fact, there was good evidence at the time that the virus did not carry its own gene for arginase, but rather turned on the enzyme found in the cells. I think that information was available when the experiment was done.

Mr. **Gore**. Dr. Anderson, you wanted to comment on this?

Dr. **Anderson**. Yes.

We finally have a point of disagreement. In the first place, in terms of what Dr. Friedmann said earlier in terms of taking a shot in the dark with a critically ill patient—I agree with him. But gene therapy is a special case. Even though somatic cell treatment with DNA is probably no different than any other kind of somatic cell treatment, nonetheless since we are still ignorant, we cannot be certain that a somatic cell DNA treatment might not inadvertently also have an effect on the germ line.

And that is why I think there is a difference between the Cline experiment and giving a patient a chemotherapeutic agent where you say let's just try it and see what happens.

As far as the Rogers experiment, I have looked into that in some detail, in fact, I wrote on the ethics of that about 11 years ago. And my disagreement with Dr. Friedmann, although I think we are really not in disagreement, is this. I think that the Rogers study was an ethical experiment at the time it was done.

What Dr. Rogers did was to do a totally open experiment in the sense that he obtained advice from everywhere possible; he asked the opinion of ethicists and theologians and scientists. It was known that this virus appeared to have no harmful effects on humans, it had been used in laboratories for years. The only effect was apparently a harmless side effect of decreasing the arginine level in the blood of laboratory workers.

Here were two critically ill patients who had high levels of arginine. Yes, it was scientifically ignorant, but this fits Dr. Friedman's category of a shot in the dark. There was no indication that there would be harm. There was a reasonable possibility that it might help. And most important, Dr. Rogers was absolutely public in this; requested an ethics ad hoc advisory committee in the days when they really hadn't been set up yet. He was totally open and postponed doing the experiment until he had input from all sides, as opposed to Dr. Cline's experiment that was done in absolute secrecy.

I think in fact Dr. Friedman and I are not in disagreement. But fundamentally I think the Rogers experiment was ethical in its time, and the Cline experiment was not ethical in its time.

Mr. GORE. Well, we are getting into the ethical implications of these experiments, and that really is a subject that we had intended to address to him. As a result, and also as a result of the fact that we have been going on a long time, maybe we ought to adjourn until tomorrow.

Let me thank the four of you for what I regard as excellent testimony, and the great help that you have given us in trying to better understand this technology.

Tomorrow we will begin with a discussion of the religious concerns, with representatives of the three groups, organizations that originally requested the study by the President's commission 2 years ago. And then we will have a number of eminent ethicists to discuss the ethical considerations. And then on the third day we will move on to societal obligations, social policy, and of course we will hear from Dr. Cline as well.

So let me adjourn this first day of the hearings by again thanking you and all of the witnesses who have appeared here today. We will reconvene at 9:30 tomorrow morning in this room. Thank you all.

[Whereupon, at 2:00 p.m., the subcommittee recessed, to reconvene at 9:30 a.m., Wednesday, November 17, 1982.]

HUMAN GENETIC ENGINEERING

WEDNESDAY, NOVEMBER 17, 1982

House of Representatives,
Committee on Science and Technology,
Subcommittee on Investigations and Oversight,
Washington, D.C.

The subcommittee met, pursuant to call, at 9:30 a.m., in room 2318, Rayburn House Office Building, Hon. Albert Gore, Jr. (chairman of the subcommittee) presiding.

Mr. Gore. The subcommittee will come to order.

I would like to welcome our guests and our witnesses today. This morning, we begin the second day of the subcommittee's 3 days of hearings on the human applications of genetic engineering. Yesterday, we heard from Prof. Alex Capron, the Executive Director of the President's Commission for the study of ethical problems in medicine and biomedical and behavioral research, who presented to the subcommittee the Commission's recently completed report on the social and ethical issues raised by human genetic engineering.

We also heard from a number of distinguished scientists, who, while they disagreed on certain specifics, all believed that the scientific ability to perform gene therapy on human beings will be upon us within the next few years.

Today, we take the next step in our effort to come to grips with all the issues raised by this new science. At yesterday's proceedings, we heard scientists' estimate of what they will eventually be able to do by altering the human genome.

This morning we will consider—from a religious and ethical perspective—some of the implications of these new-found capabilities.

Our first panel will discuss the religious concerns about human genetic engineering. Two years ago, the General Secretaries of the three major religious organizations in this country, the three largest in any event—the National Council of Churches, the United States Catholic Conference, and the Synagogue Council of America—wrote a letter to former President Carter urging a governmental review of human engineering.

That letter prompted the study by the President's Commission, about which we heard yesterday. With our witnesses today, we will explore the issues that have troubled the religious groups. For example, are scientists playing God when they begin to manipulate the genetic basis of life itself? Are scientists affecting the fundamental nature of humanity by mixing human and animal genes? What does it mean to be human? To what uses will the new knowledge be put? When is human engineering not morally justifiable?

Our second panel today will discuss the related ethical issues that are involved with human genetic engineering. As the technology continues to develop rapidly, a new push movement for human experimentation will surely arise. One issue we will consider is when those experiments will be ethically appropriate.

Moreover, we must ask whether, if the technology is proven safe for humans, it should actually be employed—and for what objectives it should be used. Should gene therapy be used to cure diseases? Should it be used to manipulate physical characteristics? What about intelligence, memory, and personality? Should it be used only on adults or also applied prenatally? How will gene defects be defined? And by whom? We will contemplate these and other issues with our group of ethicists on the second panel.

A key concern throughout this hearing is the problem of delineating the permissible and impermissible uses of human genetic techniques. It was abundantly clear from yesterday's testimony that not long from now science will have the ability to go beyond curing genetic diseases to altering the physical and intellectual traits of humans for purposes of what is called enhancement.

It is imperative that we consider the questions raised by this ability before it is too late even to ask them. It is not yet clear where the line between desirable and undesirable human genetic engineering should be drawn, but at some point a line must be drawn.

Our witnesses today can help us begin to identify that point of demarcation.

I would like to call now our first panel of witnesses, Dr. Roger Shinn, professor of social ethics at Union Theological Seminary in New York, N.Y.; Dr. Richard McCormick, director of the Kennedy Institute of Ethics at Georgetown University; and Dr. Seymour Siegel, professor of ethics and theology, Jewish Theological Seminary, New York, N.Y.

I would like to welcome you on behalf of the subcommittee and thank you for the work that you all have done in this area.

Without objection, the full text of your written prepared statements will be included in the record in full.

I understand that none of the three of you is formally speaking as a representative of the religious organizations from which you come, but it is my further understanding that all three of you have been closely involved in the deliberations of your religious organizations and that the views you express are extremely close to those expressed by the organization from which you come.

So with that introduction, let me invite you, Dr. Roger Shinn, from Union Theological Seminary, to begin our session this morning. Again I welcome you, please proceed.

STATEMENTS OF ROGER SHINN, PROFESSOR OF SOCIAL ETHICS, UNION THEOLOGICAL SEMINARY, NEW YORK, N.Y.; RICHARD McCORMICK, DIRECTOR, KENNEDY INSTITUTE OF ETHICS, GEORGETOWN UNIVERSITY, WASHINGTON, D.C.; AND SEYMOUR SIEGEL, PROFESSOR OF ETHICS AND THEOLOGY, JEWISH THEOLOGICAL SEMINARY, NEW YORK, N.Y.

Dr. SHINN. Thank you, Mr. Chairman, and I thank the committee for your invitation.

You are quite right, I am not the designated representative of any group but I have participated in many broadly based religious studies of issues in genetic science, and I think I can fairly represent a pretty wide consensus in protestant and ecumenical christian thinking.

I begin with the religious conviction that one of the gifts of human nature is the ability to create a future different from the past. The principal historic faiths of this country share the conviction that people created in the image of God, embody something of divine creativity. These faiths also recognize that human creativity often goes wrong, that intolerable evils are sometimes the intended outcome of sinful acts and sometimes the accidental consequences of good intentions.

In biological science, which is our concern today, we have seen the apparent elimination of the age-old scourge of smallpox, the reduction of many fatal and disabling diseases, the dramatic increase in life expectancy throughout most of the world. Now we are beginning steps in the genetic modification of life, including the origination of new forms of life.

Most religious communities have a basic commitment to health and to the arts of healing. The word salvation is derived from words for health and healing. Christians think of Jesus as a healer, and they have often built hospitals and fostered medical missions. Insofar as genetic practice is an extension of the arts of healing, the initial Christian response is favorable. "The burden of proof," I have said earlier, "is not on the advocacy of therapy but on its rejection."

If genetic engineering now produces insulin, superior for some patients to animal insulin, that is an advance in healing. If the modification of genetic materials someday produces vaccines against cancer, that will be a welcome achievement. If genetic therapy can eliminate some hereditary ailments without harmful side effects, that will be a blessing.

Once the general disposition to favor sciences of healing is accepted, several warnings are important. I shall mention four.

One, risks. All human life involves risk. In much medical experimentation upon people, the risks are peculiarly personal. Some experiments fail to accomplish their aims. Some actually harm people. But some risks bring benefits.

Some risks are justifiable. One standard criterion requires that, after due caution and testing prior to human application, the experimenter gain the informed consent of the subject. The neglect of that criterion has sometimes meant the victimization of poor people, of racial groups, of Third World populations—groups who are subjected to risks that more privileged people avoid.

Any adequate monitoring of risks in genetic experimentation requires careful guarding against repetition of such past abuses. And it requires special concern for the unborn, who cannot give consent.

A new study paper of the National Council of Churches states:

> Life in general and human life in particular is sacred. Research must contribute the maximal benefit for the most people, especially those least able to defend themselves.

There are many types of regulation to govern risks. A notable example of self-regulation by the scientific community was the worldwide moratorium on research in DNA from July 1974 until February 1975, while guidelines were being developed. Another form of regulation is the rules of the National Institutes of Health for experimentation by agencies funded by public money. Such regulations, except as they are voluntarily accepted by industry, do not govern commercial experimentation in this country or overseas. Hence legislative regulation may be appropriate when a public interest is involved.

Scientists, who have often experienced crude forms of external restriction, should have the maximum freedom consistent with the public good. Scientists themselves should have a voice in the formulation of regulations, but they should not have the sole voice; the public interest is not always identical with the professional interest of experimenters.

Two, misuses. The history of eugenics from Plato to the 20th century is crammed with evidences of snobbery and cruelty of dominant groups who define good heredity in terms of their prejudices. Biologist Robert S. Morison once said:

> The thing that has saved man from his limited visions in the past has been the difficulty of devising suitable means for reaching them.

As new means become available, evaluation of the visions becomes more important.

An obvious example is color of skin. A dark skin has long brought economic, political, and social disadvantages in many societies, including our own. But the liability was not genetic; it was social and institutional. Most discussions of the ethics of genetics come sooner or later to the saying of C. S. Lewis:

> For the power of Man to make himself what he pleases means, as we have seen, the power of some men to make the other men what they please.

There are hereditary ailments so obviously painful or destructive that nobody would wish them. The effort to eliminate these ailments by genetic devices is sometimes called negative eugenics, and it wins considerable endorsement. Positive eugenics, the effort to design an improved heredity, with its assumption that this generation of specialists knows what is good for all future development, is more dubious.

One international study group, convened by the World Council of Churches, heard an earnest appeal from some members to reject all positive eugenics. The group was not persuaded, but said instead:

> More fundamentally—against the day when the capability for "positive" genetic engineering may be at hand—people should be encouraged to examine, in the light

> of ethical and religious beliefs, whether the use of such capabilities would be desirable.

Three, allocation of resources. In a world where limited resources face unlimited human needs, the use of those resources reflects the values of the society. Most countries of the world can afford little or nothing for elaborate genetic research. In this country what resources should go into genetic therapies that may some day cure cancer as compared with correcting environmental causes of cancer that are operational right now? What resources should be assigned to research into the unknown as compared with correction of nutritional deficiencies for which answers are available now?

Surely research is needed. If past generations, poorer than our own, had not put some resources into research on smallpox and polio, we would be far worse off now. But the assignment of resources is proportioned less to human need than to the glamor of a project or the interests of groups who influence politics, industry, and higher education. As a result too little of our resources go to the most needy. One function of democratic government is to modify this skewing of effort.

Four, reverence for life. My final point has to do with a widespread fear which was mentioned by you, Mr. Chairman, of the manipulation of human life, a fear that technology is intruding into the personal in ways that destroy the sacredness of life. It is the fear that technologists are playing God.

In part that fear is surely mistaken. Any use of medicine or surgery can be called manipulation. A task force convened by the National Council of Churches a few years ago pointed to the biblical belief that God acts both through natural processes and through human actions. "From this viewpoint the natural may be less moral than the purposefully human act." The human effort to improve nature or to intervene with medical processes that correct natural illnesses is not necessarily arrogant or irreverent.

Still the concern will not quite die. Margaret Mead, a woman of great scientific skill and religious reverence, saw the issue more than 30 years ago. Writing about the impact of technology on human life, she said:

> Was it possible that modern man might forget his relationship with the rest of the natural world to such a degree that he separated himself from his own pulsebeat, wrote poetry only in tune with machines, and was irrevocably cut off from his own heart?
>
> In their new-found preoccupation with power over the natural world, might men so forget God that they would build a barrier against the wisdom of the past that no one could penetrate?

I do not propose that the U.S. Congress legislate reverence. But I suggest that some sense of human inviolability, rooted deeply in our national and religious traditions, may influence much that we legislate and do.

Marshall Nirenberg, cowinner of the Nobel Prize of 1969 for his work in cracking the genetic code, has written:

> When man becomes capable of instructing his own cells, he must refrain from doing so until he has sufficient wisdom to use this knowledge for the benefit of mankind.

I do not ask you to legislate that wisdom. I do ask that you use wisdom, directed to the public good, as you consider all legislation.

Thank you, Mr. Chairman.

[The prepared statement of Dr. Shinn follows:]

TESTIMONY OF ROGER L. SHINN

I thank the Committee on Science and Technology for this invitation to testify to you. I am not the designated representative of any organization, and in a sense I speak only for myself. However, I have participated in many broadly based religious studies of issues in genetic science, and I think I can claim to represent a fairly wide consensus in Protestant and Ecumenical Christian thinking.

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A new Study Paper of the National Council of Churches states: "Life in general and human life in particular is sarced. Research must contribute the maximal benefit for the most people, especially those least able to defend themselves."

There are many types of regulation to govern risks. A notable example of self-regulation by the scientific community was the world-wide moratorium on research in DNA from July of 1974 until February of 1975, while guidelines were being developed. Another form of regulation is the rules of the National Institutes of Health for experimentation by agencies funded by public money. Such regulations, except as they are voluntarily accepted by industry, do not govern commercial experimentation in this country or overseas. Hence legislative regulation may be appropriate when a public interest is involved. Scientists, who have often experienced crude forms of external restriction, should have the maximum freedom consistent with the public good. Scientists themselves should have a voice in the formulation of regulations, but they should not have the sole voice; the public interest is not always identical with the professional interest of experimenters.

2. Misuses.—The history of eugenics from Plato to the twentieth century is crammed with evidences of snobbery and cruelty of dominant groups who define good heredity in terms of their prejudices. Biologist Robert S. Morison once said: "The thing that has saved man from his limited visions in the past has been the difficulty of devising suitable means for reaching them." As new means become available, evaluation of the visions becomes more important.

An obvious example is color of skin. A dark skin has long brought economic, political, and social disadvantages in many societies, including our own. But the liability was not genetic; it was social and institutional. Most discussions of the ethics of genetics come sooner or later to the saying of C. S. Lewis: "For the power of Man to make himself what he pleases means, as we have seen, the power of some men to make other men what they please."

There are hereditary ailments so obviously painful or destructive that nobody would wish them. The effort to eliminate these ailments by genetic devices is sometimes called negative eugenics, and it wins considerable endorsement. Positive eugenics, the effort to design an improved heredity, with its assumption that this generation of specialists knows what is good for all future development, is more dubious. One international study group, convened by the World Council of Churches, heard an earnest appeal from some members to reject all positive eugenics. The group was not persuaded, but said instead: "More fundamentally—against the day when the capability for 'positive' genetic engineering may be at hand—people should be encouraged to examine, in the light of ethical and religious beliefs, whether the use of such capabilities would be desirable."

3. Allocation of resources.—In a world where limited resources face unlimited human needs, the use of those resources reflects the values of the society. Most countries of the world can afford little or nothing for elaborate genetic research. In this country what resources should go into genetic therapies that may some day cure cancer as compared with correcting environmental causes of cancer that are operational right now? What resources should be assigned to research into the unknown as compared with correction of nutritional deficiencies for which answers are available now? Surely research is needed. If past generations, poorer than our own, had not put some resources into research on smallpox and polio, we would be far worse off now. But the assignment of resources is proportioned less to human need than to the glamor of a project or the interests of groups who influence politics, industry, and higher education. As a result too little of our resources go to the most needy. One function of democratic government is to modify this skewing of effort.

4. Reverence for life.—My final point has to do with a widespread fear—of the manipulation of human life, a fear that technology is intruding into the personal in ways that destroy the sacredness of life. It is the fear that technologists are "playing God." In part that fear is surely mistaken. Any use of medicine or surgery can be called manipulation. A Task Force convened by the National Council of Churches a few years ago pointed to the biblical belief that God acts both through natural processes and through human actions. "From this viewpoint 'the natural' may be less moral then the purposefully human act." The human effort to improve nature or to intervene with medical processes that correct "natural" illnesses is not necessarily arrogant or irreverent.

Still the concern will not quite die. Margaret Mead, a woman of great scientific skill and religious reverence, saw the issue more than thirty years ago. Writing about the impact of technology on human life, she said: "Was it possible that modern man might forget his relationship with the rest of the natural world to such a degree that he separated himself from his own pulse-beat, wrote poetry only in tune with machines, and was irrevocably cut off from his own heart? In their newfound preoccupation with power over the natural world, might men so forget God that they would build a barrier against the wisdom of the past that no one could penetrate?"

I do not propose that the U.S. Congress legislate reverence. But I suggest that some sense of human inviolability, rooted deeply in our national and religious traditions, may influence much that we legislate and do.

Marshall Nirenberg, co-winner of the Nobel Prize of 1969 for his work in "cracking the genetic code," has written: "When man becomes capable of instructing his own cells, he must refrain from doing so until he has sufficient wisdom to use this knowledge for the benefit of mankind." I do not ask you to legislate that wisdom. I do ask that you use wisdom, directed to the public good, as you consider all legislation.

Mr. GORE. Thank you. That was a remarkable statement. We appreciate it. I will save questions until we have completed the panel.

I would like to call now on Dr. Richard McCormick, former director of the Kennedy Institute of Ethics at Georgetown.

Welcome, doctor, and please proceed.

Dr. MCCORMICK. Thank you very much.

I am privileged to be here. As you mention I speak as a Roman Catholic theologian, as one from a tradition but not one commissioned to speak for it.

My thoughts therefore are my own. I am happy to say that they are virtually identical with those expressed by Roger Shinn.

I believe it is accurate to my tradition to say it would approach the moral dimensions of genetic research in terms of what I call reason informed by faith, not without faith, not replaced by faith. This reason informed by faith suggests several things about genetic research and engineering.

I will be more interested in my remarks in the structure of the problem and the approach to it than outlining any right/wrong consideration.

First, it tells us that we will not find concrete answers to new questions in age-old formulations. The past must serve us but not paralyze us. Second, this tradition tells us it is specifically human to be responsible to and for ourselves. We are sharers in divine providence by providing for ourselves and others as St. Thomas put it.

This is in my judgment, the basis for a fundamentally optimistic attitude toward science and its applications.

Abuse, we can, but abuse we need not. Morally responsible people know that abusus non tollit usum, abuse does not invalidate proper use.

Three, it tells us that "we do not wrong God unless we wrong our own good." This is a citation from St. Thomas Aquinas. That means, it seems to me, that our task in these delicate matters is to discern together and discover what is promotive of human persons and their community, and what is likely to be destructive.

The approach to this last question is clarified if we try to see the general shape of a bioethical problem.

There are basic human values at stake and in play. Values such as human life, procreation and rearing of children, friendship, human identity, human freedom, and so on.

Take human life, for instance. We surround this basic value with a policy of protection and promotion and a vocabulary to communicate that policy. Protecting and promoting life, we ourselves flourish. If we fail in this task, we ourselves suffer.

When that value comes into new technological circumstances, we are forced to reexamine our previous policy and its meaning and our vocabulary. For example, resuscitation technology and respirators force us to ask ourselves what we are about when we support and preserve life. Is it mere circulation and ventilation of a body? A mere vegetative function that we treasure and support?

Some people seem to think so.

Or is it something more than that?

Similarly I believe that the technology of in vitro fertilization with embryo transfer forces us to reexamine our moral policies with respect to some basic human values. What is the importance of biological rootage to the notion of family?

What is the relation of sexual language to human procreation?

Thus the basic pattern I want to underline: basic value, new technological circumstances, new questions.

In the brief time remaining to me I would like to point out two aspects of this problem that ought to be of interest and/or concern to government.

First of all, they are substantial; second, procedural.

Substantial, at this stage of the discussion I think it is important for us individually and as a community to identify the values that are at stake as we deliberate on these matters. Some of the following occur to me and they overlap with those mentioned in the report of the National Council of Churches.

The sacredness of human life itself as mentioned by Dr. Shinn.

Two, the meaning of ourselves as social and therefore interdependent beings.

Three, the interconnection of life systems.

Four, the meaning of sexuality, the family and individual self-identity.

Five, the goals of genetic research and its environmental effects.

Six, priorities of our research effort, especially as supported by the Federal or State government. If we fail to view genetic intervention at all levels in terms of the basic values at stake we fail to assess it adequately, in my judgment. We sacrifice long-term well-being for immediate gain.

Americans are pragmatic interventionist people; they succeed now and pay later, they discover that their pesticides are carcinogenic only after having used them. We cannot afford that here.

Second, there is the process of our deliberations. Unless I am wrong, in government things tend to get done by a convoluted and compacted process involving political tradeoffs, compromise, power plays, constituent-sensitive concessions, economic cost benefit considerations and so on.

I note this in no sense of cynicism because in many areas this is the way public policy has to be hammered out in a radically pluralistic society. But it should not be this way here.

The matter is too important to be left to the ordinary political dynamic.

I am in general confident, perhaps naively overconfident in the maturity of the scientific community to regulate itself.

To repeat what Dr. Shinn said, we saw a splendid example of this in the recent moratorium scientists imposed on their own DNA recombinant research. They proved to be healthily conservative. Nonetheless, I judge it to be paramount that there be some public mechanism of ongoing deliberation and assessment of providing in this area.

Parenthetically let me add that just as the Ethics Advisory Board of the form DHEW went out of existence—it petered out of existence for lack of funding and perhaps interest—the same fate seems to be that of the current President's commission. That strikes me as being the very last thing that we ought to sacrifice as a concerned community. I think it is a scandal that these ethics advisory boards are allowed to lapse.

We need that input. The judgments to be made, the controls to be set if any, the finances to be allocated must be rooted in broad human value judgments. These do not pertain to the exclusive expertise of the scientific community.

They necessarily involve all of us because it is a common human future we are deliberating.

It is things like this that the term "reason informed by faith" would suggest.

Thank you very much.

[The prepared statement of Dr. McCormick follows:]

STATEMENT BEFORE THE SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT COMMITTEE ON SCIENCE AND TECHNOLOGY U. S. HOUSE OF REPRESENTATIVES

November 17, 1982

Richard A. McCormick, S.J.
Rose F. Kennedy Professor of Christian Ethics
Kennedy Institute of Ethics
Georgetown University

I speak as a Roman Catholic theologian, as one from a tradition but not one commissioned to speak for it. My thoughts therefore are my own. But I believe it is accurate to my tradition to say that it would approach the moral dimensions of genetic research in terms of "reason informed by faith," not *without* faith or *replaced* by faith. This reason informed by that faith suggests several things about genetic research and engineering.

First, it tells us that we will not find concrete answers to new questions in age-old formulations. The past must serve us but not paralyze us.

Second, it tells us that it is specifically human to be responsible to and for ourselves. We are "sharers in divine providence by providing for ourselves and others" (St. Thomas I-II, q. 91, a. 2). This is the basis for a fundamentally optimistic attitude toward science and its applications. Abuse we can, but abuse we need not. Morally responsible people know that *abusus non tollit usum* ("abuse does not invalidate [proper] use").

Third, it tells us that "we do not wrong God unless we wrong our own good" (*Contra gentiles* 3, 122). That means that our task in these matters is to discern together and discover what is likely to be promotive of human persons, and their community, what is distructive.

The approach to this last question is clarified if we try to see the shape of a bioethical problem. There are basic human values at stake and in play--values such as human life, procreation and rearing of children, friendship, human identity and freedom, etc. Take human life. We surround this basic value with a policy of protection and promotion and a vocabulary to communicate that policy. Protecting and promoting life we ourselves flourish. Failing to do this, we ourselves suffer. When that value comes into new technological circumstances, we are forced to reexamine our previous policy and its meaning. For example, resuscitation technology and respirators force us to ask ourselves what we are about when we preserve life. Is it mere circulation and ventilation of a body, a mere vegetative function that we treasure and support? Or is it something more? Similarly, the technology of _in vitro_ fertilization with embryo transfer forces us to reexamine our moral policies with regard to some quite basic human values. What is the importance of biological rootage to the notion of family? What is the relation of sexual langauge to human procreation? Thus the pattern: _basic value--new technological circumstances--new questions_.

In the time remaining to me I would like to point out two aspects of this problem that ought to be of interest and/or concern to the government. They are _substantial_ and _procedural_.

First, at this stage of the discussion I think it is important to try to identify the values that are at stake as we deliberate on these matters. Some of the following occur to me. (1) The sacredness of human life itself. (2) The meaning of ourselves as social (and therefore interdependent) beings. (3) The interconnection of life systems. (4) The meaning of sexuality, the family and individual self-identity. (5) The goals of genetic research and its environmental effects. (6) The priorities of our research effort, especially as supported by the federal or state governments. If we fail to view genetic intervention in terms of the basic values at stake, we fail to assess it adequately. We sacrifice long term well being for immediate gain. Americans are a pragmatic, interventionist people. They succeed now and pay later. This we cannot afford.

Second, there is the process of our deliberations. In government things tend to "get done" by a convoluted and compacted process involving political trade-offs, compromise, power plays, constituent-sensitive concessions, economic cost-benefit considerations, etc. I note this not in cynicism--because in many areas this is the way public policy must be hammered out in a radically pluralistic society. But it should not be this way here. The matter is too important to be left to the ordinary political dynamic. I am in general confident, perhaps naively, overconfident in the maturity of the scientific community to regulate itself. We saw a splendid example of this in the recent moratorium scientists imposed on their own DNA recombinant research. They proved to be healthily conservative.

Nonetheless, I judge it to be paramount that there be some *public* mechanism of ongoing deliberation and assessment of progress in this area. The judgments to be made, the controls to be set (if any), the finances to be allocated must be rooted in broad human value judgments. These do not pertain to the exclusive expertise of the scientific community. They necessarily involve all of us because it is a common human future we are deliberating.

It is such things that "reason informed by faith" suggests I submit to you.

Mr. Gore. Thank you very much. We appreciate that.

Again, I will hold the questions and call on Dr. Seymour Siegel, professor of ethics and theology at the Jewish Theological Seminary in New York, N.Y.

We ask you to proceed.

Dr. Siegel. Thank you very much, Mr. Chairman.

In addition to serving as professor of theology and ethics at the Jewish Theological Seminary of America, which is I think the leading school of its type in this country, I am also privileged to be a member of the President's Commission on Ethical Problems—it is such a complicated name I forget it.

Mr. Gore. We call it the——

Dr. Siegel. The Ethical Problems in Medicine and Biomedical and Behavioral Research.

And as a member of that Commission I of course endorse very heartily the conclusions of that Commission's deliberations which are presented to this body as of yesterday by our distinguished Director Alexander Capron.

So in that sense, I am like my friends and colleagues, I can speak almost officially as a member of that Commission although anybody who ever tried to speak for the whole Jewish community knows the terrible price that that foolish attempt usually exacts.

I want to just—I think it is a great tribute to the ecumenical movement in this country that as a Jew, I, of course, endorse everything that has been said by my distinguished colleagues and cowitnesses here. That doesn't surprise me either because we have discussed these things many times before and on other occasions.

The basic assertion of biblical religion as is indicated in the first verse of the Bible is that in the beginning, God created the heavens and the Earth. The fact that God created the world gives it meaning, purpose, and value.

The fact that it is created desanctifies the universe. The heavens declare the glory of God, they are not God himself. In pagan religion—and in some modern variations—nature is seen as sacrosanct, holy. In paganism, the gods inhabit nature—therefore, man's greatest good is to conform to nature, not to transform it.

The God of the Bible is above nature. He is not identified with any part of it. Therefore—in a magnificent phrase coined by the Talmudic rabbis—man can be a partner with God in the work of creation.

The challenge which God, so to speak makes to the human race is to use his reason, his imagination, and even what we Jews call chutzpah to wrest from nature her secrets toward the end of improving our human estate. It is this image which legitimizes the entire medical enterprise, as Professor Shinn commented before.

The double conclusion that we draw from this theological assertion is that we are bidden to thrust into the unknown to cure, improve, soothe and correct nature when it frustrates the fulfillment of the human dimension. We are forbidden to do anything either in manipulating nature, which is the other side of the coin, or in the way we organize and relate to each other which will diminish the humanness of the human being by depriving him of those aspects of life which we value as truly and basically human.

We can, and should, manipulate nature in order to enhance humanness. We dare not manipulate nature to diminish humanness. Referred to is a situation where it will certainly enhance our humanness by bringing us things we need in a cheap and easy way. The successful development of gene therapy techniques, which have not yet of course been realized in the greatest part, may make it possible to remove many congenital diseases and as an unintended though I think great outcome, will be possible for parents to discover abnormalities in fetuses and be able to correct them and keep their offspring instead of resorting to their destruction through abortion, for example.

The problem arises in the area of what is properly called genetic engineering which can be understood as applying to techniques which have as their aim the restructuring of the human species—both as to the method of its propagation and as to its genetic endowment. This could result in the manufacture of the coming generation according to specification. The prospect of modifying the genetic endowment of potential offspring and the further prospect of specifying what kind of characteristics are desired by prospective parents does present very challenging theological and ethical issues, as you heard yesterday and you will hear today and already heard from my distinguished colleagues and from those who will be sitting here at this witness table.

In an aphorism which may not be of any use, men ought not to play God before they learn to be men and after they have learned to be men, I believe they will not want to play God.

Therefore, what I am saying is as a general theological approach, we do have a human right in fact even a duty to manipulate nature in order to improve the humanness state, but we don't have a right to manipulate nature and remove from the human being those aspects which we value as peculiarly and in an invaluable way human, such as reason, free will or even the idea of risk as to the future.

These objections square with the theological chutzpah expressed at the beginning of our discussions. Surely nature is in our hands to modify and change to make this life happier, healthier, and longer. But these achievements must not be won at the price of sacrificing those characteristics of our humanity which we particularly value as being indispensible for the development of humanhood. God wants us to imitate Him, not to impersonate Him. We cannot win happiness at the price of dehumanizing ourselves and our offspring.

It is quite clear that public policy must take steps both to encourage and monitor the achievements and projects of the genetic engineers. I want to associate myself with especially Dr. McCormick, that governmental—a governmentally sponsored program body should be supported by Congress to oversee, monitor, and advise genetic engineers as to how to make this distinction which rhetorically is easy to make but in the laboratory is hard to make; namely, when are you really enhancing humanness and when are you diminishing it.

I personally have faith in these procedures, having worked myself as one of the program advising people on DNA in seeing that the partnership between the scientists and government and ethical and public community has worked to enhance an important and promising new field.

There is hope that creative cooperation between the scientific community, the public, and the Government will be able to wrest for us from nature's secrets ways to improve our life and humanhood without risking the ironic outcome of destroying our own humanhood in a spectacular effort to perfect it.

[The prepared statement of Dr. Siegel follows:]

DRAFT
6/25/82

GENETIC ENGINEERING by Seymour Siegel

Ralph Simon Professor of Ethics and Theology, The Jewish Theological Seminary of America and Humanities Fellow, Medical College of Pennsylvania, Philadelphia, PA

If the righteous desired it, they could be creators, for it is written. But your iniquities have distinguished between you and Me, saith the Lord (Isaiah 59:2)...Talmud, Tractate Sanhedrin 65b

The achievements of the human mind are seemingly limitless. If it were not for the tendency of human beings to frequently pervert stunning inventions to bad purposes, we could resemble our Creator. In the thrusts of the human spirit we practice the ancient ethical virtue of *imitatio dei*. It is the human potential to do mischief that makes his creative possibilities problematic. When humans attempt to change the character of the species radically, they can harm the human-ness of the person. What we must do as a community is to insure and encourage the development of creative possibilities while attempting to prevent dehumanization.

Before discussing some of the specific issues which are usually subsumed under the rubric of genetic engineering, let me state some basic theological assertions which emerge from the Jewish tradition.

I. Creation

The basic assertion of biblical religion is that in the beginning God created the Heaven and the earth. The fact that God created the world, gives it meaning, purpose, value. That fact that it is created--desanctifies the universe. The heavens declare the glory of God--they are not God. In pagan religion (and in some modern variations) nature is seen as sacrosanct, holy. In paganism, the gods inhabit nature--therefore, man's greatest good is to conform to nature, not to transform it. The biblical God is above nature. He is not to be identified with any part of it. Therefore--in the magnificent phrase coined by the talmudic rabbis--man is to be partner with God in the work of creation. The challenge which God, so to speak, hurls at the human race is to use its reason, its imagination, and even its chutspah to wrest from nature her secrets toward the end of improving our human estate. If anything or anybody is god-like, it is the human being who was created in God's image and who carries in his soul a divine spark. It is this image which legitimizes the entire medical enterprise. There were those in the ancient world who believed that if God sent illness, He should send the cure. This viewpoint was far from the biblical one. God may have sent the illness (even this was not certain); He wants, however, to see us bring the cure (with His help, of course).

This idea is expressed in a well-known passage from rabbinic literature.

> It occurred that R. Ishmael and R. Akiva were strolling in the streets of Jerusalem accompanied by another person. They were met by a sick person. He said to them, "My masters, tell me by what means I may be cured." They told him, "Do thus and so until you are cured." He asked them, "And who afflicted me?" They replied, "The Holy One, blessed be He." [The sick person] responded, "You have entered into a matter which does not pertain to you. [God] has afflicted and you seek to cure! Are you not transgressing His will?"
>
> Then R. Ishmael and R. Akiva asked him, "What is your occupation?" He answered, "I am a tiller of the soil and here is the sickle in my hand." They asked him, "Who created the vineyard?" He answered, "The Holy One, blessed be He." R. Akiva and R. Ishmael said to him, "And you enter into a matter which does not pertain to you! [God] created [the vineyard] and you cut His fruits from it." He said to them, "Do you not see the sickle in my hand? If I

> did not plow, sow, fertilize and weed nothing would sprout." They said to him, "Foolish man! Have you never in your life heard that it is written 'as for man, his days are as grass; as grass of the field, so he flourishes' (Psalms 103:15). Just as if one does not weed, fertilize and plow, the trees will not produce [fruit] and if fruit is produced but is not watered or fertilized it will not live but die, so with regard to the body. Drugs and medicaments are the fertilizer and the physician is the tiller of the soil."

II. The Nature of Man

Man is "but a little lower than the angels." He is the crown of creation. He, unlike all other creatures is created in God's image. His distinction above all others in the universe lies in his ability to reason, choose between good and evil, and his knowledge about himself. Only man can make himself the object of his own thought. He can imagine his death and plan for the future. He is aware of his destiny and of the possibility of relating to the Transcendant. Ideally, all should be equal; no one should dominate another human being. "For unto Me are the children of Israel servants. They were not meant to be servants to servants." Human beings have the ability to think, to communicate ideas and concepts. They have the ability to think in abstractions, to manipulate and create symbols. Man is the only creature who can tell a lie, sin. Man's freedom is the source of his ability to do the good as well as the evil. Good is the right use of freedom. Evil is the misuse of freedom. Man is part of nature, irrevocably caught in the necessities of nature, growing, perishing and dying--he is also above nature free and in touch with the Beyond. All of these and other traits, attributes and dimensions express the human-ness of the human being.

From a theological point of view we are bidden to thrust into the unknown in order to cure, improve, soothe, and correct nature to further the human estate. We are forbidden to do anything either in manipulating nature or in the way we organize and relate to each other which will diminish the human-ness of the human being by depriving him of these aspects of life which we value as truly and basically human.

With these remarks let us now turn to the specific issues usually included in the idea of genetic engineering. Part of the confusion which the public has shown results from a confusion about what it is we are talking about.

RECOMBINANT DNA

Recombinant DNA technique is a method in genetic research in which a piece of the DNA (the basic code which is found in every cell) is cut off and spliced onto the DNA of another organism. The latter organism carries its own DNA and a piece of the DNA originating in another organism. If the host organism is simple like a bacterium, the spliced-on DNA will be produced in great number. This allows for easily-acquired material for research and also a big supply of the spliced-on part of the DNA which might be interferon insulin, or some other biological substance potentially very valuable and necessary.

About a decade ago when the recombinant method was beginning to be widely used, there was a hue and a cry about the potential dangers which might follow from the creation of a new organism. Such books as Who Should Play God? by Howard and Rifkin (Dell Books) pointed up the possibility of recombining the DNAs of two organisms and thus creating an entirely new being whose properties are basically unknown.

It might happen that the new organism would escape from the laboratory and cause horrible consequences. The bacterium with the spliced-on genetic material might cause cancer, eating up of oil and other catastrophes. It is interesting to note, as has been now frequently pointed out, that the discussion was triggered by a letter which appeared in the magazine Science on September 21, 1973. The letter was signed by Maxine Singer and Dieter Soll. It was addressed to the presidents of the National Academy of Sciences and the Academy's Institute of Medicine. The letter reads in part as follows:

> We are writing to you, on...a matter of deep concern. Several of the scientific reports presented at this year's Gordon Research Conference on Nucleic Acids ...indicated that we presently have the technical ability to join together...DNA molecules from diverse sources... Certain such hybrid molecules may prove hazardous to laboratory workers and to the public. Although no hazard has yet been established, prudence suggests that the potential hazard be seriously considered.

It is interesting that on July 15, 1977 another letter emerged from the same group of scientists. An open letter to Congress was signed by 86% of the 157 members present at the meeting. The first paragraph of the 1977 letter reads as follows:

> We are concerned that the benefits of recombinant DNA research will be denied society by unnecessary restrictions in legislation.

It has been pointed out that what happened to change the mind of the scientists was the spectacular results of DNA methodology so far. There is now mass production of interferon and other important biological substances. There seem to be other breakthroughs on the horizon. Guidelines were formulated by the NIH which were followed by laboratories conducting recombinant DNA research. These guidelines mandated the way laboratories were to be constructed and what kind of organisms should be used to reduce the danger of these experiments to practically zero. The scenarios which caused so much alarm in 1973 have been precluded by the development of new types of bacteria which cannot survive outside the laboratory environment, and by the careful choosing of personnel involved in carrying out experiments. I can testify personally, as a member of the Biohazards Committee of the pharamaceutical firm Hoffmann-LaRoche, as to the exquisite care which is taken in the protection of the environment and the researchers involved in DNA experiments.

Thus it would seem that the potentially great benefits for mankind in carrying out DNA combining far outweigh any possible harm. An alert public, a sensitive scientific community and a spirit of cooperation with government have overcome the very real fears which were expressed in the beginning. Therefore, the genetic engineering expressed in the recombinant DNA technology, I believe, presents very minimal risks. We should encourage the scientists who are looking for ways in which, through this technique, mankind can benefit mightily.

Human ingenuity has probed nature; using this knowledge has improved creation and made it yield benefits for us all. Theologians, especially should not only endorse, but also encourage this line of endeavor.

GENETIC THERAPY

Genetic therapy is a form of genetic engineering which, I believe, presents very few ethical or religious problems.

In genetic therapy, the cells are repaired if there is some deficiency or abnormality. There are several types of genetic therapy possible. (See the entries on Gene Therapy in the Encyclopedia of Bioethics). One method is enzyme replacement. (See article by Elizabeth Neufeld, loc. cit.) A defect in a gene will be translated into a defect of the enzyme molecule, so "that the enzyme functions poorly." Many difficulties may ensue from the malfunctioning enzyme. It is possible to replace these enzymes with normal ones. Though the process is largely experimental and the therapeutic effects are still to be verified. Another form of gene therapy is therapy via transformation. "Gene therapy refers to the future possibility of introducing new, functioning genetic information contained in the molecules of DNA into human cells with the intention of treating human genetic disease. Gene therapy via genetic transformation would envision using isolated fragments of purified human DNA to accomplish this end." (Richard Roblin, loc. cit.) This too is at the moment highly speculative and not yet proven. Gene therapy via transduction "envisions the future possibility of using viruses or viral DNA as carriers for the introduction of new specific, foreign DNA sequences into cells for the purpose of ameliorating human genetic disease." To date experiments on human using this technique to cure genetic defects have not been successful.

It would seem that when, and if, these attempts at genetic therapy are successful and we are able to overcome genetic deficiencies by some form of genetic repairs, there would be no new ethical issues which would be different than those occasioned by other forms of medical therapy: informed consent, fair distribution of resources; etc. As a matter of fact, the successful development of gene therapy techniques might make it possible for parents who discover abnormalities in fetuses to keep their offspring instead of resorting to their destruction through abortion. Since there are possibilities that such genetic factors as gender, skin color, or height might be altered by genetic therapy, several commentators (see for example, Roger Shinn in the Encyclopedia of Bioethics c.v. Gene Therapy: ethical issues) have raised ethical questions. It seems that these possibilities--though real--are remote and therefore not very relevant to the discussion carried on today. Other discussions (see for example, Paul Ramsey, Pre-Fabricated Man) focus on the long-term effects of genetic processes. In altering gene of a fetus, for example, we are altering not only its own make up, but the make up of all future offspring. A correct gene which would make diabetes impossible in the first generation might render some harm in future generations. The human being is an integrated whole so that even a defective gene might have some salutary impact on the whole organism. Are we permitted to risk future harm for present benefits? It would seem to me that from an ethical point of view we are bidden to do as much good as we can now and pray that the long-term effects will be benign. There is an old rabbinic principle "bari vshema bari adeef--something certain and something doubtful, the preference goes to the certain." If we were sure that we are effecting genetic therapy now we should go ahead and do it even though we might think that in the future there may be some risk.

As we pointed out at the beginning of this discussion, part of the human estate and challenge is to recognize nature as unfinished and needing some improvement when that is possible. This is the theological basis for medical interventions ranging from eye glasses to pacemakers. Genetic therapy would certainly fit into this conceptual framework. Barry Commoner in promoting the ecology movement formulated a law: "nature knows best." This is said to mean "any major man made change in a natural system is likely to be detrimental to that system." (Commoner, The Closing Circle: Nature, Man and Technology. p. 41). Though this "law" seems plausible and even useful in warning against human pride (hubris), it serves a cautionary purpose not a conclusionary purpose.

GENETIC ENGINEERING:

Recombinant DNA and genetic therapy present few, if any, ethical issues. What most of the discussion is about is what could properly be called genetic engineering which can be understood as applying to techniques which have as their aim the restructering of the human species--both as to the method of its propagation and as to its genetic endowment. The new knowledge provided us by the biological revolution of our time has stimulated the imagination of our scientists. Warnings about the ominous future which awaits us and our offspring are heard on all sides. In one of the most popular books on this subject, Who Should Play God?, Ted Howard and Jeremy Rifkin warn: "well-credentialied and well-financed researchers...propose the complete retailoring of human life. Name your wildest fantasy, or nightmare, and some authority somewhere is seriously proposing it; from redesigning human stomachs so that people will be able to consume cheap hay and grass, like cows, to the hybridization of humans with lower primates. There are even some genetic engineers who eagerly await the day when their work will produce... the construction of a genetic super-race that will move far beyond Homo sapiens on the evolutionary ladder." (p. 15)

ARTIFICIAL INSEMINATION

The Journal of the American Medical Association (June 5, 1972) suggests: "the popular term, genetic engineering might be considered as covering anything having to do with the manipulation of the gametes or the fetuses, for whatever purpose, from conception other than by sexual union, to treatment of disease in utero, to the ultimate manufacture of a human being to exact specification. Thus, the earliest procedure in genetic engineering is artificial insemination, next...artificial fertilization...next artificial implantation...in the future corporeal gestation... and finally, what is popularly meant by genetic engineering, the production or better biological manufacture of a human being to desired specification."

The process of artificial insemination was mentioned by the rabbis as early as the fifth century of the common era (See Jacobovitz, Jewish Medical Ethics). In general, Jewish ethicists have endorsed artificial insemination by husband (AIH) without question. There has been some controversy about artificial insemination by donors (AID) (see Bleich, Judaism and Healing, index, artificial insemination). Those who opposed AID did so on several grounds: 1) possible incest, since the donor is not known there is a remote possibility that siblings might marry in the future and 2) possible adultery. If the seed of another man is placed in the body of a woman already married it might be viewed as adultery 3) the unseemly act of treating conception mechanically and artificially. Expressing the strong pro-natalist viewpoint of traditional Judaism, AID was accepted as a means of making possible the procreation of children. The latter seems to be the majority view of the decisors. This is, of course, limited to married couples. The Jewish viewpoint would not accept the artificial insemination of a single women or certainly of lesbian couples. This would be seen as a strong blow against the idea of the family, a basic pillar of the Judeo-Christian social outlook. In general, all of the proposed genetic engineering feats are to be viewed against the background of "family impact." The mere production of children is not enough of an excuse to go ahead with new technology. The raising of children is always seen in the context of the family unit. One could foresee many problems which would affect family relationships. What new forms of sibling rivalries will develop among children who share the same mother but have different semen donors for fathers? How will children (or the wife) relate to the male figure who is present in the home but has no biologcial function in the birth of the children. There are also legal problems regarding inheritance and personal status. Notwithstanding these problems, the Jewish tradition is so pro-natalist and so highly valuing of the place of children in a family that it is willing to risk the difficulties and accept the good consequences. Again, it is important to stress that this viewpoint is to be seen against the background of the traditional family. Jewish ethics and morality would look askance at the encouragement of biological procedures would would tend to weaken the traditional family.

TEST TUBE BABIES

The conception of a fetus outside the body of the mother is a phenomenon which was recently accomplished. The moral question involved is to be seen in the light of the viewpoint that to have children is a great commandment (Mitzvah). As long as the couple itself is involved there seems to be no moral objection. "There would be no objection to joining sperm and ovum of a married couple in a test-tube or a petri dish" (Siegel, S., The Jewish Week, July 14, 1978). There have been objections raised to "test tube propagation" because of the fact that all the ova are not properly fertilized. Only one is chosen to be replaced in the body of the woman giving the ovum. What happens to those fertilized ova which are not healthy enough to be reimplanted? Is this a form of abortion? Such highly respected ethicists as Professor Paul Ramsey have raised this question. It seems to me that even if one were to be opposed to abortion, the destruction of fertilized ova outside the body of mother and before they have become attached to the uterine wall would not come under the category of abortion. Therefore, whatever considerations there might arise, the question of abortion would not be one of them.

Another consideration, which is of great importance, is raised by Dr. Leon Kass of the University of Chicago. (See Restak, R., Pre Meditated Man: Bioethics and the Control of Future Life., p.63). "What is new about embryo transfer is a divorce of the generation of new life from human sexuality ultimately from the confines of the human body. Sexual intercourse will no longer be needed for generating new life. This novelty leads to two others: there is a new co-progenitor, the embryologist-genticist-physician; and there is a new home for generation, the laboratory. The mysterious and intimate processes of generation are to be moved from the darkness of the womb to bright (fluorsecent) light of the laboratory."

The same objection is raised by Professor Paul Ramsey (Fabricated Man): "Many of these proposals would irreversibly remove a basic form of humanity: the basis in our creation for the covenant of marriage and parenthood." What Ramsey is saying is to be taken very seriously. Part of our humanhood is that we are made biologically for parenthood by joining togeher with another human being in the production of a third human being. This biological fact, argues Ramsey, is part of spiritual legacy, which is a unity of the biological and the non-biological. It is also part of our human legacy to have a realization in the depths of our own consciousness that we have come into the world through the union of two human beings, who, uniquely are involved in ourselves. The developments of techniques like in vitro fertilization call this into question. "Human parenthood is, in the language of Karl Barth (one of the greatest of the Protestant theologians of the twentieth century) a basic form of humanity. To violate this is already dehumanizing." (Ibid, p. 31) By mechanizing the process of procreation we are about to deprive ourselves and our progeny of a profoundly human dimension. Therefore, theologians such as Ramsey and philosophers such as Kass argue that we would be better off as a species if we stopped the developing the enterprise before we go too far.

These arguments are very convincing and serve as a necessary warning against excesses. It would seem that they would be more applicable in a situation where the artificial means of conception were to be used outside the conventional family attachments: such as for single women or with sperm stored for a long time of individuals who had achieved some distinction, such as Nobel Prize winners. This kind of biological mechanism, especially if it were to become widespread, would certainly pose a threat not only to the traditonal family, but to the basic character of the human species and human parenthood. However, it seems to me, if AID or test tube propagation, is employed within a context of the traditonal family which would continue to nurture and establish a strong bond with the offspring which are brought into the world, then the threats to the fundamental nature of human parenthood would be minimal, if present at all. The warnings against "thing-i-fying the carnal life" should be taken seriously and form an important part of our considerations concerning genetic engineering.

HOST MOTHERS

Of special interest are recent experimental developments which indicate that it may soon become possible to remove a naturally fertilized ovum from the womb of a pregnant mother and to reimplant it in the uterus of another woman. The embryo would then remain in the womb of the "host-mother" through the period of gestation until birth.

Rabbi Immanuel Jacobovits, Chief Rabbi of Great Britain, characterizes such practices as offensive to moral sensitivities when resorted to as a convenience in order to avoid the difficulties of pregnancy. (Jewish Medical Ethics, second edition, appendix). "To use another person as a "incubator" and then take from her the child she carried and delivered for a fee is a revolting degradation of maternity and an affront to human dignity." (David Bleich, Judaism and Healing, p.92). Besides these considerations, there are other difficulties of a more technical nature such as, who is in truth the mother of the child, who are siblings, etc.

In general, we would have to employ the criteria stated previously. While we wish to encourage the production of children in families where nature makes this sought-after end unattainable, we should be extremely cautious in encouraging procedures and developments which would endanger the preservation of the family.

So far the issues with which we have dealt have been relatively easy to solve. If nature frustrates the legitimate desires of married couples for children, then it seems licit to "outwit" nature so that fertility can be achieved. This all within the parameters of preserving those aspects of our humanity which we particularly cherish and value, such as parenthood, while be careful about the "family impact" of newer ways of conception and gestation.

The theological and ethical issues become very difficult and complex when they involve procedures where the coming generation will be manufactued "according to specification." These procedures are in various stages of experimental development. They range all the way from cloning of humans to specifying the sex of the child to be conceived; specifying his physical or mental characteristics. As the technology develops, even leaders as Doctor R. G. Edwards admit that his research on in vitro fertilization "provokes various thoughts and opinions: the beginning of test tube babies, armies of carefully planned robots (and) playing God in the laboratory." (cited in Rifkin, op. cit., p.109)

The prospect of modifying the genetic endowment of potential offspring and the further prospect of specifying what kind of characteristics are desired by prospective parent(s) does present very challenging theological and ethical issues.

As usual, Professor Paul Ramsey has put the issue in dramatic focus: "Men ought not to play God before they learn to be, and after they have learned to be men they will not play God." Parents would be seen as consumers, alternately selecting and rejecting various possible variations in children. Those who wish only blue-eyed children, for instance, might someday be provided with the technology needed to bring this about. (See Richard Restack, op. cit., p. 78)

This dramatic and unprecedented modification of the next generation brings in its wake profound theological and moral questions. The central question is that man ceases to be a creature and turns instead to being a creator. Can genetic engineering legitimately be used to realize mankind's most cherished and persistent hope: of creating a perfect world without sickness, travail, endurance, and ultimately without death? Are we dealing with what Ramsey calls "a messianic positivism." The corruption of the present world will be overcome not by faith and trust in a beneficent God but in the stupendous achievements of biological scientists. No longer would love and self-sacrifice, a kind of awesome uncertainty about the future, test and refine human character, but trust would be placed in the biological messiahs who would fill orders for people who would want a prefabricated person.

How do these observations square with the theological chutzpah which was expressed at the beginning of our discussion? Surely man is a "little lower than the angels." Surely, nature is in hands to modify and change to make his life happier, healthier, and longer. But these achievements must not be won at the price of sacrificing those characteristics of our humanity which we particularly value as being indispensible for the development of humanhood. God wants us to imitate Him, not impersonate Him. We cannot win happiness at the price of dehumanizing ourselves and our progeny. What gain will it be if we gain perfect genes and we lose our souls. By all means we should encourage genetic and other types of research to remove disease to make procreation within the family context possible where because of a quirk of nature it is now impossible--but we should restrict and restrain ourselves in the search to recreate our own species. The myth of Frankenstein has its origins in the Jewish myth of the golem. The great rabbi Loew of Prague, who lived in the sixteenth century created a golem, a lifeless lump to whom he gave life using mysterious kabalistic procedures. When the Rabbi's community was being threatened by a murderous mob, the golem turned on the attackers and defeated them. However, since the golem had been unleashed, he could not stop and turned on his creators. The great rabbi turned the golem back into dust. Will our stupendous achievements with which we can conquer our perennial enemies, in the future turn upon us? Will we be able to turn them back into dust?

It is quite clear that public policy must take steps both to encourage and monitor the achievements and projects of the genetic engineers. Some body will have to be chosen and given the task of regulating activities in this exciting and awesome new field. There is hope that creative cooperation between the scientific community, the public, and the government will be able to wrest for us from nature's secrets ways to improve our life and our humanhood without risking the ironic outcome of destroying our humanhood in a spectacular effort to perfect it.

Mr. GORE. Thank you very much, Dr. Siegel, for a very thoughtful statement. All three statements have really been extremely helpful.

I hesitate to oversimplify, to try to encapsulate what you are saying and do damage by oversimplifying, but I am struck, and I invite your comments, I am struck by the fact that all three of you seem to endorse the idea of full speed ahead so long as we are cautious and if we enhance rather than diminish humanness, then there are no theological problems that the three of you really are that concerned about.

Does anybody disagree with that?

Dr. SIEGEL. I would be concerned if we stopped it. I would like to put it even stronger than the chairman did, that if we have the opportunity to do something so revolutionary, and so impactful, helping people, that we not do it because of some theological caution.

Dr. MCCORMICK. I agree with that. I think one of the things we have to contend with in the public discussion of these matters is a segment of the community which I am not prepared to identify, but I encounter it, a segment of the community which basically approaches any scientific breakthrough, especially one that touches human persons, with a predominant attitude of fear, born out of perhaps personal characteristics, born out of reflection on the past experience, and so on. As I understand the testimony, all three of us are saying that that is an infection that should not be allowed to intrude.

Mr. GORE. Dr. Shinn.

Dr. SHINN. Yes, Mr. Chairman.

In your nice way of putting it, I would think that sometimes the caution might mean half-speed ahead rather than full-speed ahead. I think it would mean a "no" to some experiments that have been conjectured.

I think the example of Nazi medicine and the treatment of human beings is a warning that some things are wrong.

Mr. GORE. Yes.

Dr. SHINN. But I say that as a qualification in what was a basic affirmation of investigation in this area.

Mr. GORE. I find that very, very interesting.

Dr. McCormick, you referred to a fear that many people have of new developments in science. You know the record is not all that good in some resports if you look, for example, at the creation of nuclear weaponry.

For example, if we had developed a fuller understanding of the implications of that technology at the time it was invented or created, surely we would have made greater efforts to build a different world than the one in which we now live.

Maybe the concern that many people feel about this technology is to some extent justified and it is up to us to dispel those fears by demonstrating that we as a Nation, we as a society, can deal with this technology more carefully and responsibly than nuclear weapons have been dealt with.

Dr. MCCORMICK. I hope we have learned in that experience several things. As you perhaps are aware, the history of development of atomic weapons was accompanied by no little dose of conscience problems by those who developed them, as you can read in books like "Brighter Than A Thousand Suns," and so on. But I suppose by the nature of the historical experience, the public could not participate at that point in the discussion of these things. We were in a warfare situation.

I want to use that as an example for repeating—and as strongly as I can—that we need to have vehicles for public discussion. That is the only way we will get controls that I think will divide the human from the inhumane here.

Dr. SIEGEL. Mr. Chairman, may I underscore this very important objection of Father McCormick. I think people who cry wolf, or whatever they cry when it comes to these matters and related matters, have hidden agendas which I think is the duty of all of us to uncover.

They may be antigrowth, anti-American, anti this or that, antibusiness, antiscience for whatever ideological reasons, and whatever the scientist does may reflect that in a kind of mad scientist symbol which some of the media project, both printed and other kinds of media. I think we should face the matter as it is, not from behind the hidden agenda.

Second, that I think we cannot underestimate the experience of the DNA recombinant episode here in which there was the same kind of hue and cry that this was going to be worse than the atomic bomb, this would destroy the world by eating up all the oil in the world or whatever.

You have read all these doomsday scenarios that came forth. Now, these were not altogether bad, but they were certainly not altogether good. They did result in this kind of interplay of the scientific community, the public community—that is, the public as a whole—and the Government.

The result was there was a check and balance in each one, and I think in this particular episode it showed a surprising conservatism and caution, which I think was of no small measure, and which led to good results.

In addressing some scientists I say in my experience the scientists were at least as moral as my own colleagues, which I thought was a high compliment to both.

Mr. GORE. Well, thank you. I have other questions that I would like to come back to, but I would like to recognize now one of the ranking members of our full Science and Technology Committee, Congressman George Brown.

Mr. BROWN. Thank you, Mr. Gore.

I am sorry that I missed a good part of your earlier statements, but I want to indicate the importance that I attach to this subject matter and the contribution which you gentlemen have made to it.

I think too many of our political intelligence scientific decisions have not been imbued with any considerations of values and fundamental human concerns. This hearing this morning begins to focus us in that direction. I think you all have made valuable contributions to that.

Dr. McCormick, I was pleased with your statement, but I wonder what degree you consider it to be representative of the religious community, the Catholic community, or the Society of Jesus.

Are you some sort of freak speaking out on this subject or what? Are you presenting the viewpoint which you might call a consensus viewpoint on this subject?

Dr. MCCORMICK. Well, I am certainly not a freak, if Roger Shinn and Dr. Siegel agree with me in substance, but I stated earlier that I think the matter is so complicated that none can confidently speak as one commissioned by tradition. One can only speak as one influenced by tradition and informed by it.

I feel, from past discussions with my colleagues, reasonably confident that the perspectives I would present on these matters would be a fairly characteristic thing of a mainline approach to them. We might state our cautions in different ways, we might state our presumptions in different ways, but I think it represents a consensus.

Mr. BROWN. I seem to have a recollection that the Pope has spoken at least peripherally on this subject from time to time. Can you refresh my memory as to the thrust of what he has been saying?

Dr. MCCORMICK. He has spoken a couple of times that I remember to groups of scientists. I can only recollect in a general way, but his statements were statements of support and of caution; basically, in a general way of approaching the matter, that we can abuse, yes, but we need not.

Mr. BROWN. I was struck by a couple of articles that appeared in the press just in the last few days, the last one this morning, having to do with the death of an eminent, almost saintlike figure in India, who left this life on his own initiative.

He was very old, he had a heart attack, he knew that he didn't have many more years, and he refused any life-supporting equipment and chose to die, even though the Premier personally pled with him to accept help to extend his life.

That struck me as being representative of a moral dilemma that is confronting us more and more as we find technology intervening in the process of human life. I think it accentuates the point you made in your remarks about the need to rethink some fundamental values that we have in looking at these problems.

I am not sure I have a question in bringing that up, but this business of maintaining life for people who have lived a full and fruitful life and probably have no more to contribute is yet another side of this coin, I guess, of genetic and biological manipulation, which we are becoming more and more expert at.

I wonder if you have had any reflections about this ethical area, or is there any relationship between that and what we are talking about here in terms of manipulating human life at the initial stages?

Dr. McCormick. Is that question put to me, sir?

Mr. Brown. I think so, yes.

Dr. McCormick. I think there is a definite connection between the two problems. The way we solve the problems that we currently are facing, for example, in care for the terminally ill. The way we face them is a paradigm of the way we will face problems of a different nature involving different values.

The very type of moral reasoning we use, the very type of openness, the type of discipline we bring to these problems is going to be descriptive of the way we approach other ones. So, methodologically there is a continuity.

There is a continuity also in the fact that in all of these cases we are dealing with human life itself, and if we have basic attitudes of reverence which take concrete form in the treatment of the terminally ill, they are going to reappear in these areas, or if we are a little cavalier in care of the dying, interventionist and so forth, those are going to appear here, too.

There is continuity both in methodology and substance, in my judgment.

Dr. Siegel. I just want to say, Mr. Brown, that the Commission on Ethical Problems in Medicine, in the report of genetic engineering, the next report will be on the care of the terminally ill. I recommend it to you very much.

Mr. Brown. I will be interested. I am sure you know that more and more families are having to make decisions involving whether to allow a loved one to end their life or not.

Dr. Siegel. Of course.

Mr. Brown. But because of the miracles of modern technology that question arises. As Dr. McCormick says, that is a decision that has to be made with a certain amount of reverence, and reverence is not the sort of thing we do very much good in legislative areas.

Many people, despite their nominal religious attitudes, don't even know what reverence means. That is one of the reasons I think this is such a valuable hearing. We are confronting some issues that are not customarily confronted in this kind of a forum.

I have no further questions.

Mr. Gore. Thank you very much.

Congressman Harold Volkmer of Missouri.

Mr. Volkmer. I have no questions for the witnesses. I, too, am sorry I was not here earlier, but I wish to commend the chairman for holding these hearings and believe that it brings us more information about the processes that are coming about in genetic engineering in the next several years. I think it is most informative.

I, too, wish to thank the witnesses for their information, and I will review their statements.

Thank you very much, Mr. Chairman.

Mr. Gore. Thank you.

Let me ask a few more short questions.

You make the distinction, Dr. Siegel, between enhancing humanness and diminishing it. What criteria would you use to distinguish between the two?

Dr. Siegel. Well, as I said, it is a difficult question, which doesn't mean it doesn't have some answers.

Mr. Gore. Is it like the Supreme Court's definition of pornography: you know it when you see it?

Dr. Siegel. I think the Supreme Court would be the last piece———

Mr. Gore. Is it like one of the justice's statements about pornography: You know it when you see it, even if you can't define it?

Dr. Siegel. There are obviously some values or dimensions which are obviously good for you in health, lack of debilitating diseases, congenital abnormalities. Therefore, to remove those would seem to be laudable; in fact, I think a responsibility if we could do it.

There are some things like—I would say that an individual having two parents that he knows that he or she had been produced through the love of two human beings to whom he can always go is something which is an important part of the humanness.

Mr. Gore. Suppose that was not done? It is theoretically possible.

Dr. Siegel. Not yet. It will be, yes.

Mr. Gore. Yes.

Dr. Siegel. I would say that if we were able to, as we will be able to, I think, arrange for the whole procreational process to be done outside of anybody's body, everything from conception to birth, I think that that would be something that we should be very careful about and without—just an intuition—I would say we shouldn't do that.

That would make production—even the word I am using, production—that would make the birth of new human beings so mechanized, so unhuman, that it would be bounding, in my judgment, to affect the human self-understanding of the individual who would result from that.

Mr. Gore. Would you prohibit it?

Dr. Siegel. Well, I would think very seriously of prohibiting it and also think very seriously of the consequences of prohibiting it.

Mr. Gore. What theological question would it raise?

Dr. Siegel. It would raise the question of what is a human being, the one you raised at the beginning of your remarks. Is a human being a being produced by mechanical means or artificial means totally, or is a human being at his most basic, fundamental character an essence or a being who is himself the result of two other human beings deciding or at least getting together to produce him.

Therefore he always can—I think there are at least two other people—or one, because sometimes the father is unknown—at least one person to whom he or she has some organic relationship which nothing can sever.

Mr. GORE. Would you make that an essential part of the definition of human being?

Dr. SIEGEL. Yes, I think so.

Mr. GORE. You would be concerned about anything that violates it?

Dr. SIEGEL. I would be concerned about any perfection of a procedure in which the total process would be mechanical or artificial.

Mr. GORE. Anyone else?

Dr. SIEGEL. That is not a good example. Obviously free will, you know, you read all these scenarios about people creating a kind of human species that wouldn't have free will, so they could be our servants and we would not have to pay them very much.

Those are, of course, obviously the kinds of things we would not want, or something that would be half human and half horse or something like that, mixing the species.

Mr. GORE. That should be prohibited?

Dr. SIEGEL. Mixing the human species with another species certainly should be prohibited.

Mr. GORE. Dr. Shinn?

Dr. SHINN. Mr. Chairman, I think we can all point far out there to some possibilities that would be abhorrent——

Mr. GORE. Yes.

Dr. SHINN [continuing]. Aldous Huxley's "Brave New World," George Orwell's "1984." The problem is in the intermediate area, what things are going to enhance life and what are going to be destructive of what is most important about being human.

That is very difficult. That is the reason why I didn't want to prescribe everything but would endorse what my colleague said explicitly, and I did not, some continuing government way of keeping informed on this, not poking in it every point along the way, but making everyone aware there is a public interest in this.

Now, let me give a particular example that shows the difficulty of the question that you have raised so well. This comes out of the study group that I did refer to gathered by the World Council of Churches in 1981.

It was reported that in certain experiments a few human chromosomes and proteins have been introduced into a live mouse. Nobody seemed to be greatly disturbed by this. On the other hand, there are proposals for the mating of a chimpanzee and a human being, which again theoretically is possible and may prove possible in practice, to produce a new species somehow subhuman, and there was a general abhorrence of this.

Now, I think I can see reasons why the first case doesn't bother people a lot; the second does. That does not mean I am ready to draw the precise line between what is dehumanizing and what is enhancing human life. We have to continue working on that.

Mr. GORE. Yes. Well, the ease with which you all approach the technology I thought if you get a little bit below into projecting out into the future, of course you will become uneasy, as we all will very soon.

What about another line of possibility, and that is that traits might be selected for children for reasons that have to do with the preference of the parents. Is that all right, within the theological traditions you represent? Dr. McCormick.

Dr. MCCORMICK. I want to return to a distinction that Dr. Shinn made between negative eugenics and positive eugenics. You are dealing, as I understand your question, with positive eugenics, the systemmatic breeding of superior genotypes and so forth, and virtually every commentator that I have read in the scientific community, the ethical theological communities runs from that problem as if it were a plague. It is the scenario full of dreadful problems.

Mr. GORE. Yes.

Dr. MCCORMICK. What criteria do you use? Is technical intelligence better than emotional, moral sensitivity? Who decides these things? One of the major problems that I would think that sound religious tradition, almost any, would bring to that question, would be this, that when we begin to program people for certain definable characteristics, say superior intelligence, as they are now doing in that looney bin place out in San Diego—the Repository for Germinal Choice.

If you start doing that, something very subtle happens to you as a human being and as a society because you are beginning to evaluate human beings not for who they are but for what they can do, their function. In other words, you are reducing the whole to a part, and a society which begins to do that can begin to do some awfully uncivil things, discard those who don't meet certain levels, and so on and so forth.

I would hope we all could agree on that type of extreme caution.

Mr. GORE. Yes.

Dr. MCCORMICK. With regard to anything like positive eugenics.

Mr. GORE. Prohibit it?

Dr. MCCORMICK. My own feeling is that there should be clarity enough in many of the areas that are envisaged by positive eugenics to say that we are close to being able to make that a public policy of some kind or another.

I don't think we should try to have public policies where they aren't necessary. We should rely on self-regulation and things like that. I feel pretty certain most scientists are going to do that.

Mr. GORE. Yes.

Dr. MCCORMICK. Again, perhaps I am naively overconfident.

Mr. GORE. Dr. Shinn.

Mr. SHINN. If I may reply to your question, Mr. Chairman, I think all parents try to impose their values and preferences on children. Now, in part, this is a responsible thing. It is what rearing children means, but I think all of us hurt our children at some point by overdoing it.

Now, if we get a new power to do it genetically as well as by education, there are great risks in it. Some of them are of an obvious scientific nature. Theodocious Jazansky, a great geneticist of a generation past, has written: "Would anybody know what would be better for mankind centuries or millennia hence? No, heredity is good, regardless of the environment."

If we try to construct the heredity of the future, we may unintentionally incapacitate them for dealing with different situations, and this is the reason I would exercise great caution. I would not absolutely forbid eugenics because I do not think technically it is possible to define the difference precisely between positive and negative eugenics.

As you could say, a very low IQ, to try and correct that would be negative eugenics, to try to improve an average one positive. Where is the line? So much of this has got to be in the area of commonly accepted wisdom of the society rather than of strict prohibitions, and yet I think there may be places where it is thoughtfully decided some things just shouldn't be done, and should not be allowed.

Mr. GORE. In your statement, Dr. Shinn, you did not discuss the prenatal genetic diagnosis and the problems involved there. Do you think that prenatal genetic screening is desirable?

Mr. SHINN. It is going ahead at a very great rate, and the number of diagnosable ailments is increasing month by month. The procedure usually involves the determination whether there is a serious ailment or not, and if there is, the parents have the option of abortion. Now, abortion is an issue that in general isn't on the agenda today.

Mr. GORE. No, and I don't wish to raise it, because——

Mr. SHINN. I think it is related to genetics at this particular point.

Mr. GORE. Yes.

Mr. SHINN. I know a good many people who would say if abortion is ever justifiable, it is to prevent the birth of a really tragically disabled fetus. They would make an exception there even though generally they are against it. The difficulty is that this is going to be a rather late abortion, not a first trimester one, a rather late one, and to do it for trivial reasons seems to me dehumanizing.

For instance, when—as is happening in a few cases, not many—parents choose to abort a fetus because it is not the sex they desire, I really think that is dehumanizing.

Mr. GORE. Yes.

Mr. SHINN. It is somehow to say—it usually happens to be a feminine one, not always but usually a female one. To say that this is a genetic disability and that fetus should be denied birth—I think that is really dehumanizing.

Mr. GORE. Yes, and should serve as a warning that there may be other abhorrent uses of that technology.

Dr. SIEGEL. Mr. Gore, what Roger just said is kind of an interesting theological question which reflects on the one that you asked before, namely, that part of being human is living in an unknown or unpredictable future, and that prefabricated man—to use the title of a very good book, by Paul Ramsey—although it might superficially look like a good thing that you could be sure that your offspring are this or that, blue-eyed or black-eyed or going to be big enough to be basketball players or what not, or to be male or female, might sound like a good thing. But part of being human is to have this kind of element of the unknown surround us.

Mr. **Gore**. Let me ask a question that may sound a little fuzzy or not well focused, but let me try it anyway. All three of your traditions tell us that man is created in the image of God. What do you mean by the image of God, and at what point do your traditions tell us that that image is or should be inviolable?

Dr. **McCormick**. Well, you used the word "fuzzy" question. I don't think it is a fuzzy one. I think it is one demanding of a voluminous answer, and in the time we have I am not sure one can do it.

Mr. **Gore**. We have a tradition here of allowing people to revise and extend for the record, if you want to.

Dr. **McCormick**. One can go in about 50 different directions. One can begin with, for example, "male and female He made them" and then begin to develop that, the imagery of God, the image of God as found in the diversity of sexes, complimentary, and so on.

Another way is to follow the route of those who say that God is not simply the Creator of our order, but he is the enabler of our possibilities. One is a rather static picture. God puts you there. There is nature, don't touch it. It is an incomplete symbol of what God is, in my judgment. God is not only that, but He is the enabler of our growth potentials and so on.

Mr. **Gore**. The present and the future possibilities?

Dr. **McCormick**. Yes. You know one can set up any number of scenarios that build on that notion of image of God and carry them in a number of ways.

Mr. **Gore**. Dr. Shinn.

Mr. **Shinn**. There have been centuries of literature on the subject, and to sum up my opinion very briefly, I would say this figure of speech stands for human freedom, creativity, purposefulness, esthetic and moral capacity, and anything that diminishes these is dehumanizing.

It strikes at the element of divinity in the human being, and the fears which we all want to reject but which we see reasons for are that somebody may try to turn people into mechanisms, produce them like cars coming off assembly lines, feed this into the computer and you get this paint job and you feed this and you get another one and then you have quality controls at the end and you scrap those that don't make it, and you can eliminate compassion, a certain amount of what Lionel Truitt once called that "wildness of spirit" which is our grace to believe is part of being human.

Now, I have sometimes been greatly bothered by the "wildness of spirit" in my own children, but in the end I treasure that, you see, and I would not want to control their lives, whether by social means or by genetic means so as to crush that. We are on the edge of the great mystery of what it is to be human here, and that is how phrases like "reference for the sacredness of life" do not have precise definitions, certainly cannot be legislated, but do infuse our whole system which believes that human beings have inalienable rights, the whole notion of a democratic society.

Dr. **Siegel**. I think one of the signs of the image of God is the fact that people know that, that the consciousness of human beings, that they are created in God's image. That itself is an expression of being created in God's image. That is a Talmudic statement.

That is why it is a little convoluted perhaps, and when people, for reasons that we have been talking about now for the last hour or so, lose that sense, either by somebody acting upon them or something that they do to themselves of their own specialness as human beings, then they have lost something that is indispensable for their own growth and potential.

Mr. GORE. Well, thank you very much.

Let me just sum up by saying that I understand the three of you to be telling us that you would like to see some governmental body keep track of the developments in this field, monitor them and focus our awareness onto the bioethical implications of the work that is being done. But as of now, when you scan the horizon and look at the implications, you see no—well, that does an injustice to your statements by contracting it so as to distort it.

You have given very thoughtful statements and outlined some areas of concern, but in general you have said if it is handled carefully, this is something that can enhance or improve tne loss of those who are suffering from illness and enhance our lives in other ways. And your statements have been very, very helpful. I wish to thank you for your courtesy in coming and sharing your ideas with us.

The three groups from which you come, let me say again for the record, were the three organizations that requested the study by the President's Commission, and if there are other groups in the country, religious groups that wish to state views, we would be delighted to have statements included in the record of this proceeding.

Thank you very much for your courtesy, and good day.

Dr. SIEGEL. Thank you, Mr. Chairman.

Mr. GORE. Our second panel and the final panel of today's hearing is on the ethical considerations involved here. The panel is made up of Dr. John Fletcher, assistant to the Director for bioethics at the National Institutes of Health. If you would come and join us at the witness table. Dr. LeRoy Walters, director of the center for bioethics at the Kennedy Institute of Ethics at Georgetown. Dr. Richard Zaner, professor of medical ethics, Vanderbilt University School of Medicine in Nashville. Dr. Jonathan Beckwith, professor of microbiology and molecular genetics at Harvard University Medical School in Boston.

Gentlemen, I am delighted to welcome you here on behalf of the subcommittee. We are looking forward to your statements. Without objection, the full text of your statements will be included in the record in full at this point.

Dr. John Fletcher, assistant to the Director for bioethics at NIH, I would like to welcome you and ask you to begin.

STATEMENTS OF DR. JOHN FLETCHER, ASSISTANT TO THE DIRECTOR FOR BIOETHICS, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MD., DR. LeROY WALTERS, DIRECTOR, CENTER FOR BIOETHICS, KENNEDY INSTITUTE OF ETHICS, GEORGETOWN UNIVERSITY, WASHINGTON, D.C., DR. RICHARD ZANER, PROFESSOR OF MEDICAL ETHICS, VANDERBILT UNIVERSITY SCHOOL OF MEDICINE, NASHVILLE, TENN., AND DR. JONATHAN BECKWITH, PROFESSOR OF MICROBIOLOGY AND MOLECULAR GENETICS, HARVARD UNIVERSITY MEDICAL SCHOOL, BOSTON, MASS.

Dr. **Fletcher**. Thank you, Mr. Chairman and members of the subcommittee, for inviting me. Mr. Chairman, the views that I offer today are my own. I have collaborated with Dr. W. French Anderson for more than 12 years in studying, teaching, and writing about ethical issues, especially in prospective human gene therapy.

My remarks concern two types of prospective gene therapy. The first, "gene therapy" will likely see fragments of DNA used as therapeutic agents in a few single gene disorders like thalassemia. This therapy will be directed toward changing somatic cells within tissues like bone marrow or liver.

I will also give some ethical reasons for and against a prospect of "gametic correction," that would alter the human sex cells to prevent genetic defects.

Animal research in this second area has been both promising and troubling. Scientists have already shown that correction of a genetic defect in fruit flies by DNA insertion into the germ line was inherited by the progeny. Experiments with mice and other animals continue to raise the possibility of gametic corrections as a way to prevent some genetic disorders in humans, if it ever became feasible and safe.

My purpose in discussing arguments about gametic correction is not to persuade toward a final position. This prospect is so distant in humans, in my view, that it is not wise or even necessary at this time to take a final position. But we can examine the actual situation in which it might arise, the arguments for and against it, and whether any public policy action is needed.

Genetic interventions raises ethical questions for all persons, and even fear for some. Physical, ethical, and metaphysical dangers have been widely discussed.

Advances in genetic knowledge raise many ethical questions about those consequences and proper guidance. The immediate moral dangers of gene therapy which should cause us to be skeptical until proven otherwise are possibly harmful, that is, cancer-causing mutations that would be harmful and would be inherited.

These dangers are researchable, and will be mainly answered by experiments in nonhuman species. The long-range ethical questions about gene therapy are, where will it take us? This is the issue of goals and unintended consequences. And second, will the power to modify genes threaten basic human values and ethical systems?

As the subcommittee heard yesterday, a sound scientific basis for gene therapy does not exist today. Therefore, any experiments in gene therapy would be by definition unethical. If this basis were firmly established, my argument is that additional ethical reasons exist to support initial trials in gene therapy.

A sound body of research ethics has evolved in the past 30 years to guide the conduct of physicians, patients, and families that will be involved. The problems to be faced will be no different in kind than those now being faced in experimental fetal therapy and neonatal medicine.

A reliable decisionmaking process, namely, institutional review boards, is already in place to consider the ethical problems of using gene therapy for the first time. This process was good and reliable, but Dr. Cline defaulted by not keeping faith with it when he attempted gene therapy in 1980.

There are additional ethical reasons to support gene therapy, however, beyond the fact that it could be done, if it were scientifically possible. First, there is a moral obligation to seek the means to relieve the vast burden of suffering from genetic disorders. In the United States, at least 1 in 10 individuals, or over 20 million persons, will have or now have a genetic disorder.

Approximately 15 percent of this total burden is made up of single gene defects, that is, monogenic defects. This is a very large percentage of this total burden. We must not resign ourselves to suffering and the harms of pain and premature death inflicted by these disorders. The obligation to relieve and prevent suffering within the boundaries of human ethics is the central organizing principle of medicine.

Other ethical reasons to support gene therapy stem from present methods of prenatal diagnosis of genetic disorders. In the last decade, as techniques were introduced for prenatal diagnosis, something like a promise was made to our society, and repeated, that the effort to uncover fetal disease and deformity would be followed by attempts to treat and cure these conditions.

The moral reasoning of many pioneers of prenatal diagnosis was that, if a lethal or serious and untreatable genetic disorder was diagnosed in the fetus, the parents should be morally supported whether they chose to terminate the pregnancy and tried again to have a child of their own, or chose to proceed with the birth knowing the risks. Parents who made either choice could be supported. Gene therapy might be an answer, along with new medical and surgical fetal therapies that would balance prenatal diagnosis with more therapeutic measures.

Also parents who seek genetic services during pregnancy normally want a child very much. The choice to abort a desired pregnancy is a moral dilemma that causes much anguish in itself, and it is clear that abortion is not therapeutic for the fetus. If gene therapy were truly successful, some of the harms of later abortion in desired pregnancies would be reduced and perhaps prevented altogether.

How might the prospect of gametic therapy really arise in the future? In my view, a span of 50 to 100 years is necessary to envision how gametic correction in humans could serve ethically acceptable medical aims. Assuming that gene therapy were successful, physicians will follow the first generation of patients carefully for any complications that might arise. We might also expect that other forms of medical and surgical therapy will develop that over other options.

In this future, more affected, but treated persons will live longer and have more children with the expectation that they could receive some kind of therapy, including gene therapy.

We might also presume that scientists showed that genetic defects in animals could be routinely changed by means of gametic correction.

Many generations of animals would be followed to show that the benefit was inherited by the progeny with no harmful consequences.

If these ideal conditions became actual, human gametic correction in the zygote or at least stages of life might become a reasonable or a realistic and arguable prospect.

The strongest ethical argument for it, if it were feasible and in conditions like these, is to prevent genetic disorders at their source.

Given these advances, not only could many recessive disorders be so prevented, but also some X-linked and dominant disorders.

The strongest arguments against gametic correction have social, ethical, and metaphysical reasons. Critics like Leon Kass and Paul Ramsey have repeatedly stressed that gametic corrections would likely lead to unforeseeable genetic dislocation and damage to future generations; misadventurous experimentation, for its own sake and without consent, on the well-being of individuals yet to be born; experiments with ectogenesis or growing the zygote beyond the embryo stage, and manipulated in experiments of ectogenesis; a precedent for positive eugenics and genetic engineering to attempt to improve traits like intelligence, memory, lifespan, or to reduce aggression or other traits considered troublesome.

Mr. GORE. Let me interrupt you briefly to say some may have trouble with the word "gametic." What you are referring to is surgery or gene procedures on gametes.

Dr. FLETCHER. On gametes, the human sperm and egg, the sex cells of the father and mother, those cells that produce the human being.

Mr. GORE. And at what point would that procedure take place?

Dr. FLETCHER. The only point that I have seen in the literature discussed envisioning it would be in the very first stages in the human zygote, in the first few days of life.

Mr. GORE. After conception and before cell division had progressed very far?

Dr. FLETCHER. That is right.

Mr. GORE. And one of the implications that you are pointing to is the distinction between genel therapy on the somatic cells which affect a single individual, and on the germ line cells which means that it would be passed on to future generations. That distinction is not present when you are talking about a gamete at that early stage, is that correct?

Dr. FLETCHER. That is right.

Mr. GORE. All right.

Dr. FLETCHER. You are talking about the original——

Mr. GORE. Whatever you do is going to be passed on when that gamete grows into a child and is born and has children?

Dr. FLETCHER. It is highly likely.

Mr. Gore. All right. Go ahead.

Dr. Fletcher. The writers who have given reasons to oppose gametic correction tend to present it as a doorway to serious threats to human values and to ethical systems themselves.

They claim that if this power were used, and these consequences followed, human beings who were loyal to ethical systems as we know them today would not be able to recognize themselves as humans.

In other words, life would be dehumanized.

These are serious objections. I certainly take them seriously. However, objections can be offered to the dire apocalyptic picture that is behind it. I believe that our society is resourceful and strong enough to guide genetic knowledge now and in the future on a firm medical course, allowing it to be used only to correct well-defined genetic disorders.

This is, in fact, the course that human genetics is on today. The vast majority of commentators in science and ethics oppose a use of gametic correction or any other type of genetic knowledge for eugenic proposes to try to create a "better race" of humans.

Gametic correction has little future except in a strictly medical context, if ever, and we should not close our minds to a distant possibility to relieve suffering, even if generations of work and debate might lie between ideal and reality.

Mr. Chairman, my argument is that sufficient ethical wisdom now exists to use somatic cell gene therapy in the best interests of persons.

An adequate decisionmaking process also exists. Nothing resembling this state of affairs exists for gametic correction.

This subject and others related to distant use of genetic knowledge need to be patiently studied, debated, and distilled for public policy considerations.

Whether special safeguards are needed to prevent improper and untimely genetic experiments with human gametes and the human zygote is a subject for rational debate in an optimal setting.

Dr. Grobstein of the University of California in San Diego has called for a governmental body, a body appointed by Congress, and the President's Commission has too, to study, monitor and weigh the social and ethical significance of new advances in genetic technology and to make appropriate recommendations about public polls to Congress and other agencies.

I believe these proposals have great merit.

I do not view the prospect of gene therapy as an ethical crisis or an emergency. The prospect beyond the first trials of gene therapy may, however, present alternatives of genetic changes that would further modify patterns of human reproduction in very significant ways.

There's both the time and the obligation to consider these matters and the public's best interest in the most optimal way. Thank you, Mr. Chairman.

[The prepared statement of Mr. Fletcher follows:]

ETHICAL ISSUES IN PROSPECTIVE HUMAN GENE THERAPY

Statement prepared for the Investigations and Oversight
Subcommittee of House Science and Technology Committee

Hearings to be held November 16-17, 1982

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ETHICAL ISSUES IN PROSPECTIVE HUMAN GENE THERAPY

Introduction

I give below an ethical argument for a type of human gene therapy that will likely see fragments of DNA used as a therapeutic agent. If it is scientifically feasible, the therapy will be directed towards somatic cells in human tissues like bone marrow and liver. The goal of the partners in this experimental therapy will be to correct the faulty expression of genes within these cells. I shall call this prospect "gene therapy."

I also explore some ethical reasons for and against a prospect of "gametic correction." Gene therapy of the type already mentioned would be secondary, since somatic cells develop originally as results of the pairing of parental chromosomes in sperm and egg. Genetic errors encoded on the chromosomes of these sex cell, the gametes, directly give rise to some genetic disorders. In many others, the environment interacts with the gene in question in an eventually harmful way. External fertilization (*in vitro*) of the human zygote makes possible the prospect of deliberate gametic correction, but the beginning of life is not the only time it might be attempted.

My main purpose is to show that valid ethical reasons exist to support gene therapy, if and when it becomes scientifically feasible. My goal is discussing gametic correction is not to persuade, at this time, toward one or the other poles of the argument, but to clarify questions and issues that need to be addressed in an optimal debate. I hope to contribute to the consideration of the ethics of research with or alteration of human germ cells, especially in the human zygote.

I begin the discussion with a historical perspective human understanding of genetic disorders and the development of moral aims about the use of knowledge about human genetics.

Human Genetic Disorders in Historical Perspective

The earliest societies to keep records (Babylonian, Assyrian, and Egyptian) believed that birth defects were to be taken as portents, events that were useful to predict good or evil for the group in which they occurred.[1] The word "portent", "monster", and "prodigy" came into English from Latin roots that were based on this theory of supernatural origins. Another popular theory was "maternal impressions." A sudden shock or fright was believed to produce defects. Positive impressions, however, could produce healthy children. In ancient Sparta, expectant mothers were ordered to gaze at statues of Castor and Pollux to make more perfect babies. Birth defects were also associated with theories of demons and witches. Many unfortunate parents of newborns with malformations were persecuted and killed for this reason. A hybridity theory developed that accounted for some defects due to coupling between humans and animals. For example, in the New Haven Colony in 1642, an innocent one-eyed servant named George Spencer was executed after being found guilty of the birth of a one-eyed (cyclopic) pig with a gigantic snout, which was clearly an accident of porcine genetics. The reaction of the colonists, however, was to blame it on the human who most resembled the malformed animal.

In the 19th century, Mendel's work on the laws of heredity and Darwin's theory of natural selection that best explained the history of species led to more scientific and testable theories of genetic and environmental causes of disorders of human growth and development.

After Darwin, the late 19th and early 20th centuries saw the rise of an unscientific and harmful form of ideology, Social Darwinism.[2] Biological issues were confused with the economic process, and the "survival of the fittest" was wrongly taken to justify class and social distinctions. Further, Social Darwinist thought influenced unjust law on sterilization and immigration.[3] Memories of the exaggerations of Social Darwinism and the racist-eugenic programs of the Nazis continue in literature, films and public discussions of human genetics.

The subject of intervention in human genetics stirs up controversy, feelings of resistance and partiality, and is initially opposed or questioned by most persons who consider the prospect. If one asked the theretical "person-on-the-street" for a reaction to proposals to replace faulty genes with DNA to correct the message, the response would likely touch on cloning, chimeras (mixed species), or the spectre of a "superrace." Why are there such strong feeling and statements?

o The scientific aspects of human genetics are still poorly understood in society, by many of its leaders, and only recently has been taken seriously by physicians. Education in biology and genetics is generally brief and poor.

- The prospect of intervention evokes distorted images of "meddling scientists" combined with disillusionment and fear of the environmental consequences of technology.
- Popular culture's discussions of cloning and chimeras dominated the discussion of human genetics in the early 1970's and displaced the more central topic of gene therapy.
- Memories of the earlier, discredited theory of eugenics persist and are exacerbated by disputes about sociobiology, genetics and IQ, and an elitist proposal for spermbanking and artifical insemination to spread the genes of Nobel laureates.
- The evolution-creationist controversy is very strong in some regions, which clouds rational discussion and creates fear and misunderstanding of human genetics.
- Because genes are such a fundamental aspect of what makes us human, any prospect of deliberate change raises the issue of power over others as well as knowledge about the physical basis of the human species.
- Because some hold supernatural explanations for genetic disorders and the reproductive process itself, genetics touches on a "mystique" strongly akin to religious loyalties.
- The present practices of genetic screening, counseling, and prenatal diagnosis, for all of the good purposes served in giving parents knowledge and choice about at-risk pregnancies, are still involved in the controversial abortion issue.

- Finally, many scientists themselves have counseled the greatest caution about deliberate interventions in the genes of humans and other forms of higher animals until it was known with something approaching virtual certainty that little or no harm to future generations would occur. In this light, the National Institutes of Health (NIH) guidelines about the experimental use of recombinant DNA represent a significant degree of local and national oversight of the newest genetic technology, but no feature of the existing guidelines specifically treats applications in humans.[4]

These ideas, memories, and conflicts combine to cloud the prospect of gene therapy with various levels of physical and metaphysical concern. My task is to separate those moral dangers of which we should be rationally afraid from fears of metaphysical confusion that are understandable because of the bridge between the known and unknown that may be crossed by gene therapy. There is no precedent for deliberate modification of human genes, although there occur limitless modification of genes through environmental influences, drugs, and chemotherapy.

The immediate moral dangers of gene therapy, which should cause us to be skeptical and even fearful until proven otherwise, are of possibly harmful (carcinogenic/teratogenic)consequences of genetic interventions. I believe that these questions are researchable and will eventually be answered by experiments in non-human species.

The long-range ethical questions about gene therapy are:

(1) Where will gene therapy take us? (i.e. the issue of goals and unintended consequences)

(2) Will the power to modify genes threaten basic human values and ethical systems? (i.e. the source of metaphysical fear and confusion)

These long-range ethical and metaphysical concerns can best be addressed, in my view, by patient debate of the issues guided by two commitments:

(1) A commitment to reason, which means that the best scientific evidence is relevant to the issues.

(2) A commitment to be loyal to many (not only one) ethical principles and traditions of human ethics to guide social and individual action. Complex ethical problems require the help of many expressions of ethical concern to find practical guidance for society. Therefore, an openness to compromise and incremental steps are a necessity.

My central argument throughout this statement is that, given a sound scientific basis for gene therapy, we are morally obliged to learn how to modify human genes because of the great suffering that might be relieved or avoided. As I look to the distant future and imagine the account that our generation will have to give about our moral choices in genetic experiments, my main fear is that we will not be able to give rational ethical reasons as to why we did not educate ourselves about human genetics, learn to alter the molecular origins of single-gene disorders, and possibly help multitudes of future persons with the problem of suffering and premature death. I hold that we should be less afraid of facing new generations who asked, "Why did you take the risks to learn how to correct genetic disorders?" than risk the question, "why you did not make the effort to learn whether it could be done?"

Scientific Feasibility and Ethical Wisdom

In 1967, Marshall Nirenberg, who with others pioneered the translation of the genetic code, portrayed the moral problem raised by his and others' discoveries:

> The point which deserves special emphasis is that man may be able to program his own cells with synthetic information long before he will be able to assess adequately the long-term consequences of such alterations, long before he will be able to formulate goals, and long before he can resolve the ethical and moral problems which will be raised. When man becomes capable of instructing his own cells, he must refrain from doing so until he has sufficient wisdom to use this knowledge for the benefit of mankind.[5]

This passage describes the familiar moral tension between scientific feasibility and ethical wisdom applied to the novel prospect of deliberate modification of human genes. When will it be ethical to attempt gene therapy for the first time? In the years since 1967, scientists have learned even more about the art of DNA-directed change in the genes of bacteria, plants, and animals. So much progress has been made that informed scientists like Anderson[6] and Grobstein[7] believe that attempts at somatic gene therapy may be feasible in the near future, perhaps in two or three years. Yet, no solid scientific basis now exists for attempting this kind of therapy, because no evidence is available from animal experiments that the newly introduced gene can:

- make enough product (e.g. normal betaglobin) to be effective
- remain in the appropriate cells long enough to be helpful
- not cause greater harm (e.g. malignancies) to surrounding cells or to subsequent offspring than the benefit it produces (e.g. correction of the defect).[8] (Presumably the results of somatic cell therapy would not be inheritable, if the sex cells are not affected and the new genes remain in the somatic cells.)

A realistic view of the future of somatic gene therapy must take account of both impressive and troubling results of animal experiments. Scientists have microinjected new DNA into the mouse embryo and offspring can be found that inherited the DNA that expressed into RNA and protein[9]. However, the exogenous DNA cannot yet be targeted to exact gene sites and sometimes becomes unstable. A recent report from Dr. Frank Ruddle's laboratory at Yale Univesity is that offspring of a mouse embryo injected with DNA became sterile.[10] However, work in Drosophila (fruit flies) recently showed that a visible genetic defect in the eye color in one strain of the species was corrected by introducing a new DNA fragment into the germ line. The correction was inherited by the progeny.[11]

If animal experiments could not meet the three criteria posed above, gene therapy ought not to be attempted in humans. Such experiments would be unethical. However, to make my argument, I must assume that a scientific rationale for experimental somatic cell therapy will be eventually established. In our society and many others, however, because a human experiment is feasible is not considered an ethically supportable reason why it ought to be done. In research ethics, as in general social ethics, "can implies ought," but "can" does not determine "ought." Science cannot dictate ethical directives. Even successful animal experiments do not, in themselves, constitute overriding ethical reasons to begin human experiments. Human beings make moral choices by selecting from various pre-ethical or ethical premises.

I shall not trace here the evolution of research ethics and practices in modern nations.[12] However, some features of this history will clarify the problem originally posed by Nirenberg, but now better subdivided into two possibilities: the prospect of modification of autosomal cells and gametic cells. Would it be ethical to attempt modification of these types of cells?

When moral questions arise, persons usually seek guidance (and they ought to) from within the most trusted and reliable moral forms and loyalties they have learned. Moral forms and loyalties evolve in a social process. The process of moral evolution produces forms appropriate for moral deliberation and a body of content to guide the work. Just as variation can be found in "nature," so can it be found in morality. There are myriad forms and uncountable codes and bodies of rules. However, variation should not deter responsible persons from their tasks. The first question is about the most fitting form for decision-making to "get at the problem." If we leap directly to the content of the problem without asking about the best way (form) to use to work on it, we risk moral blame. I intend by the term "content" to point to what Nirenberg doubtless meant by "wisdom," namely, a reliable body of standards, norms and principles acceptable to the group as a whole by which to guide decision-making. Having selected a more or less fitting form in which to consider the problems, persons then work on its content. Moral considerations fall into two parts: 1) factual assessments of the means and consequences of alternatives, and 2) consideration of relevant norms and standards that apply to these assessments.[13]

Until the mid-1960's the prevalent and preferred form for consideration of the primary ethical issue in human experimentation (i.e., when is it ethical to begin?) was the counsel of the investigator's scientific and medical peers. Society was apparently content,until the 1960's, to trust the judgment of scientists themselves. A series of ethical disasters,[14] and the advent of more powerful drugs. transplantation, and research tools like recombinant DNA strongly influenced policy makers towards more impartial and community-based considerations of human experiments. A new form of prior group consideration evolved that included more interdisciplinary and lay (non-scientist) participation.[15] By public debate and discourse, a new body of ethical wisdom or content gradually emerged, composed of clearer standards and norms for the conduct of review and research. The ethical principles that were widely accepted as normative to guide research were clarified and pressed upon all conscientious persons who engage in research.[16] An ethics of research had become differentiated from the ethics of medicine. In many ways the former is more articulated than the latter. The content of research ethics was carefully translated into operational standards for prior group review, the protection of vulnerable research subjects, and the conduct of research itself. These standards have the force of regulation in Federally sponsored research,[17] and are widely accepted as the norms of practice in privately sponsored research.

During the past decade (1970-1980) there also developed a stronger emphasis on the moral value of the scientific merit of the experiment and the reliability of the risk calculations prior to human trials. Although science cannot dictate ethical premises, basic ethical premises now strongly influence the scientific preparation for an experiment. The experiment must be designed to maximize learning and benefit to subjects. If the experiment is not truly feasible and it involves more than minimal risk, the investigator and reviewers would be doubly blameworthy in the event of harm and little or no learning. A standard near scientific perfection clearly operates on trials of gene therapy in animal experiments.

Scientific and Ethical Issues in Two Cases of Attempted Gene Therapy

Two previous attempts of gene therapy have come under scientific and ethical criticism. These cases illustrate well the maturation of the ethical significance of prior group review of human experimentation. Further, one can examine historically how basic ethical issues in human gene therapy have been addressed and are likely to be addressed in the future.

Between 1970 and 1973, three German sisters who suffered from hyperargininemia were unsuccessfully treated by injections of Shope papilloma virus.[18] The disorder, hereditary lack of the enzyme arginase, led to excessive amounts of arginase in the sisters' blood and severe mental retardation. Experiments with rabbits showed that infection of skin with Shope papilloma virus stimulated the synthesis of arginase. Further, the arginine concentration of some laboratory workers in who worked with the virus showed lower concentrations than those of hospital patients used as controls. The first animal experiments were done in 1958. "Peer review" discussions about the feasibility of treating two then affected sisters were conducted between 1966 and 1969. A third daughter was subsequently born and also injected with a very small dose of the virus.

In 1972, Friedman and Roblin objected to the experiment as "premature" because of unanswered scientific questions and risks.[19] They also commented on "ethics" in an indirect criticism of the viral experiment's principal investigator, Dr. Stanfield Rogers:

> For an acceptable genetic treatment of a human genetic defect, we would require that the gene therapy replace the functions of the defective gene segment without causing deleterious side effects either in the treated individual or in his future offspring. Years of work with tissue cultures and in experimental animals with genetic defects will be required to evaluate the potential side effects of gene therapy techniques. In our view, solutions to all these problems are needed before any attempt to use gene therapy in human patients could be considered ethicallly acceptable[20]

No scientist directly criticized Dr Rogers as"unethical". Friedman and Roblin defined the basic problem as procedural or technical. They wrote that scientists and physicians involved in the arginase deficiency experiment illustrate a "tendency to use incompletely genetic manipulative techniques, borrowed from molecular biology, in clinical settings."[21] Writing at the time that only two sisters had been treated, Anderson[22] described the experiment as "a preliminary type of gene therapy" justified because of the "tragic circumstance of the case involved." However, Anderson was concerned that "success here might encourage less justified attempts at premature gene therapy." Apparently, as a physician he could have conscientiously done the experiment had he been in the place of Dr. Rogers. At least, he was unwilling to cast moral blame on Rogers. In these years, the ethos of therapeutic research was probably less perfectionistic in science and prone to give the physician the benefit of the doubt in administering first-time treatment to suffering patients. The proposal to treat the German sisters was vigorously discussed for several years by Rogers and European physician-colleagues. It was not submitted to a process of prior group review as it is known today.

Ramsey, an ethicist, disagreed with Anderson's reasoning, reversing it to state his position:

> Precisely because of these tragic circumstances, the experiment seems to me unjustifiable. Dr. Anderson supports his position with a question: 'If you were the parent of a newborn baby who was found to have argininemia and therefore to be doomed to suffer and die, would you allow your baby to be exposed to this relatively unproven technique of gene therapy?' Under the conditions Dr. Anderson described there would be little question of moral

> justification; that would clearly be a case of gene therapy. Severe retardation, suffering and death would be in prospect, and the virus treatment, though unproven, would be the only recourse.[23]

Ramsey stressed that the clinical situation of the two German sisters was different from that of a hypothetical newborn. The older sister was profoundly affected by the disease, and in Ramsey's view, she was only a research subject unable to benefit but available for study. He objected to her inclusion in the trial. He was more open to a trial for the younger sister in whom the disease had not progressed as far. The choice of subjects in this experiment was an unexplored ethical issue. The public debate about this issue took place after the trial rather than beforehand. This choice and a reasonable scientific doubt about whether the induced arginase was coded for by viral or cellular genes would likely have been more thoroughly discussed in the context of prior group review.

A third affected daughter was treated at a younger age but with no therapeutic effect. No other efforts to use the Shope papilloma virus as a therapy for this disorder have been made or planned.

The first genetic experiment, like the second, was conducted outside the United States (for completely different reasons) but not subject to any requirement for prior group review. The first case was nonetheless discussed and reported in the open climate of medical-scientific publications and professional meetings. Dr. Rogers, the principal investigator, acted openly, with the aim to deliver an unknown but somewhat promising agent to suffering patients. Previously, this kind of action had been done and praised many times in medicine and research. My own inclination is also not to cast moral blame at Rogers. Contrary to Ramsey's interpretation of the situation of the older child, events proved that she did improve somewhat, although Rogers stated that it was unknown whether a larger dose of the virus or a low protein diet was the source of improvement.[24]

The second case occurred in 1980 when Dr. Martin Cline attempted to treat bone marrow by gene therapy, following irradiation, in two patients in Italy and Israel who suffered from a hereditary blood disorder. The patients apparently were not worse or better due to the experimental procedures. His choices and subsequent actions were openly judged by scientists[25] and subsequently by the NIH[26] to violate scientific and ethical standards of research with human subjects. Cline ignored data from his own work on mice that showed little scientific basis to believe that globin gene insertion in humans would succeed. Further, he deceived his institution's human subjects' review group, his medical colleagues, and his patients by failing to inform them that he would use a form of recombinant DNA restricted by guidelines of the NIH The guidelines required prior approval by the Institutional Biosafety Committee of Cline's university There was a shadow of bad faith over the second case that does not appear in the first, and it is less difficult to assign moral blame.

This latest unfortunate but real chapter in the history of gene therapy is instructive ethically and scientifically. Dr. Cline was dealt with severely by his university and the NIH. The former withdrew his chairmanship of a department, and the latter chose to withdraw some current grants. Subsequent reviews of grant applications begin with a report of his breach of research ethics. Clearly, our society is more demanding ethically and more unforgiving towards erring academic physicians than towards one in the practice of medicine who attempts an "innovative" procedure with subsequent harm to patients. However, it is notable that in the development of new forms of experimental fetal therapy, investigators in the United States, Canada and Great Britain regularly submit their plans to prior group review.[27]

Ethical Reasons for Gene Therapy

At least three ethical reasons support experimental gene therapy when, and only when, there is duly attained consensus by a review body that a proper scientific rationale exists.

First, there is a moral obligation to seek the means to relieve the vast burden of human suffering from genetic disorders. In the United States, at least 1 in 10 individuals, or over 20 million persons, now have or will develop inherited disorders. These disorders account for 25 to 30 percent of admissions to children's hospitals.[28]

Specifically, what is the burden of monogenic or single-gene disorders in the spectrum of congenital malformations? A report prepared for the Steering Committee for the Five Year Research Plan of the National Institute of Child Health and Human Development stated:

> Known congenital anomalies can be divided generally into two categories. Those in the first group have an etiological history, albeit poorly known in most instances. This group comprises 35 percent and has as a basis either genetic aberrations (15 percent), chromosomal aberrations (10 percent), or environmental insults (10 percent). Thus, a significant grouping of congenital anomalies can be shown to have a cause-and-effect relationship, but only a relatively small proportion of these (environmental insults, 10 percent) lend themselves to alleviation by intervention. For the second group, or the remaining 65 percent, there is no known etiological history, and their causes remain hidden in probably malfunctioning processes of normal development. In keeping with its major role in regulating normal development, the nervous system is involved with the largest percentage of congenital anomalies (33 percent), and one-half of all lethal anomalies involve the nervous system.[29]

The best current estimates, therefore, are that 15 percent of congenital disorders arise directly from monogenic causes. A recent report of the World Health Organization stated that in two single gene defects, sickle cell disease and thalassemia, there are over 100 million carriers and that approximately 200, 000 children die each year from the consequences of the disorders.

We must not resign ourselves to suffering and the evil inflicted by genetic mutation that is harmful and perhaps preventable. The obligation to relieve and prevent suffering, within the boundaries of human ethical systems, is the central organizing principle of medicine. Although human suffering is ubiquitous, we ought to regard it as an evil in itself or as an "intrinsic" form of evil. Physical and mental suffering is evil in itself without being compared to anything else. There is some comfort in being told that things might have been worse when we suffer. We may even feel that we are better in some ways for having suffered. From the standpoint of ethics that should guide society's considerations of medicine and other pursuits of the relief of suffering, it is always better if injury and suffering do not happen. The individual and the world would be better off without it. As philosopher David Griffin expressed this view,[30] there is a difference between holding the idea that genuine evil is necessary (in the sense of inevitable) and holding the idea that the possibility of genuine evil is necessary. It is not inevitable that evil always accompany the good that can be done. But it is inevitable that the possibility of evil will always be present.

A second ethical reason for gene therapy is to fulfil a promise. As techniques were introduced for prenatal diagnosis during the past decade, the promise has been repeated that the effort to uncover fetal disease and deformity would be followed by attempts to treat and cure these conditions. One could say with no hesitation that such was the moral reasoning of the pioneers of prenatal diagnosis.[31]

Recently, the opportunity to treat the fetus in utero and after birth, following prenatal diagnosis, has increased.[32,33,34], In addition to some medical and surgical measures must be added the hope that gene therapy will also be a means to treat the fetus, newborn, or developing child. It is plausible to assert a moral obligation to provide medical treatment to a fetus. If something can be done to help a fetus in distress and the therapy is proven, it follows that it ought to be done if the risks to the mother are acceptable. If harm can be prevented by proven therapy, including gene therapy, more balance would have been restored to the ethics of prenatal diagnosis and to medicine.

The obligation to act on the promise to seek therapeutic measures for genetic disorders is also heightened because of technical progress in prenatal diagnosis.

Stephenson and Weaver[35] compiled 182 fetal conditions now diagnosable prenatally. Virtually all known chromosomal disorders are open to diagnosis by mid-trimester amniocentesis. Ninety-six percent(96%) of all prenatal diagnoses provided knowledge that the fetus was not affected. It is likely that more fetal lives are thereby saved than in a period before this knowledge was available.

Research on new methods to retrieve and grow fetal cells may lead to alternatives that avoid the risks of fetal loss, prematurity, and maternal injury associated with needle puncture of the uterus and amniotic sac. Kazy and associates[36] in the Soviet Union, reported results of chorion biopsy in 165 cases between 6 and 12 weeksof pregnancy. Most of the women had requested early abortion. Diagnostic results were 100 percent accurate for 26 pregnancies at risk for six-linked disorders. No infections or amniotic sac disrptions were seen in this experiment. (The report contains no mention of the informed consent of the subjects.)

Perhaps the most significant scientific advance in prenatal diagnosis is the use of fetal DNA as a vehicle for diagnosis in hemoglobin disorders.[37,38] As more is learned about the human gene map, linkage studies may provide indirect markers for genetic disorders not yet diagnosable. Further, there is a potential for early retrieval of fetal cells from maternal blood separated by use of a fluorescence-activated cell sorter.[39] Technical problems remain in methods to culture fetal cells at this stage. Also fetal cells from a previous pregnancy circulate in the mother. If these problems are solved, early diagnosis as a result of safer methods will shorten the time now required to analyze cultured cells.[40]

These rapidly developing movements in diagnosis and knowledge about human genetics will likely exceed the ability to treat genetic disorders for many years to come. However, strong efforts are needed in research on gene therapy, first in animals (and if successful), then in humans. Technical achievements such as "gene-mapping" will make it likely that something resembling a "biopsy of the genome" will be available in the future. More knowledge will be available about where harmful genes are located on the human chromosomes. Persons will likely want to know more about themselves genetically. It would be clearly unethical to proscribe this knowledge. The possibility of gene therapy will ameliorate the possibility that more genetic knowledge will be interpreted in a negative rather than positive way. If something positive can be done to address the harm that genetic mutations do, persons will likely use this knowledge constructively rather than continue to condemn or blame themselves.

In summary, trends in research and development of prenatal diagnosis will probably lead to: 1) continued improvement of existing methods, 2) an increasing number of diagnosable disorders, 3) safer alternatives to amniocentesis and fetoscopy, and 4) earlier diagnostic results.

The third ethical reason that supports gene therapy is to reduce the harms of late abortions in desired pregnancies. As a consequence of the opportunity to treat the fetus in distress and to view it in the role of patient, the moral status of the previable, treatable fetus will increase.[41] From one point of view in ethics, what could be done technically to help a fetus should have no influence on its moral status. The value of a fetus, in this view, should not depend on anything extrinsic to it, such as parental desires for a child or the state of the art of fetal and reproductive medicine. This form of reasoning has a weakness and a strength. The weakness is that, when applied to a fetus with a serious and diagnosable disorder, it would prevent taking action to relieve tangible suffering of the parents, family, and others. The strength of the argument is that the developing but affected fetus in unavoidably a living individual whom we ought to help, if we had the means, because of the good that could be done for its life chances. To reach this goal will require many years, even generations, of study, research, and appropriate therapeutic experiments with the human fetus.

Abortion is not therapeutic for the fetus, as critics like Ramsey remind society.[42] The harm of death is sometimes done to fetuses that might have a mild form of a disorder with a wide range of severity, such as spina bifida and sickle cell disease. Further, normal fetuses are rarely but regrettably lost in the risks of amniocentesis, although this risk barely exceeds the risks of fetal death under normal conditions. However, in the light of the reasoning I advanced earlier, it would be better for that fetus if that harm did not occur at all. In the present context, parents and their physicians choose between two types of harm, which ought to be reduced for ethical reasons.

Late abortions are more risky for the mother in terms of mortality and morbidity.[43] Additionally, because parents who request genetic services normally desire the pregnancy, they tend to suffer from depression and often require psychiatric treatment[44] if a positive diagnosis is followed by abortion. The moral dilemma faced by parents in this situation is accompanied by anxiety and grief for the lost child-to-be.

There is little question, in my view,that the fetus in the period following prenatal diagnosis (19-23 weeks) possesses some characteristics that rational persons would accept and recognize as necessary to be a human self, e.g.

- o a recognizable human form
- o a functioning brain and central nervous system
- o responsiveness and more complex feelings that can be understood as "sentience."

Grobstein [45] recently characterized these qualities as uniqueness, integralness and imminence of self. These characteristics are relevant to the moral question about the differences between abortions in late mid-trimester and decisions about deliberate non-treatment of newborns with the same degree of impairment. Does the former make the latter more plausible?

I have held in the past that there is a crucial morally relevant difference between the fetal and the newborn context, [46] namely, that the fetus' interests are inextricably interwoven with the autonomy of the mother, and the newborn is a separate individual who deserves full protection. This difference, however, centers more on the mother's interests than fetal interests. The opportunity to reduce the need for abortion in late mid-trimester would likely relieve some of the threat, felt by critics of abortion, posed towards malformed newborns and other handicapped individuals. This threat is primarily moral in nature, I point out, because studies of actual practices in newborn intensive care units show ample evidence that physicians are very active in attempting therapy for the most seriously damaged newborns.[47]

Ethical Wisdom and Gene Therapy

In the light of Nirenberg's appeal, I have argued that sufficient wisdom or ethical content now exists to guide the use of gene therapy for the benefit of humankind, on the condition that scientific criteria described above were truly met. The ethical reasons offered above could be accepted by traditions that span religious and non-religous sources of inspiration. These reasons can reconcile some of the concerns of those with loyalties toward early fetal life with those committed to the moral priority of the relief of suffering.

Further, there is already an adequate form for moral consideration of the appropriate time to begin gene therapy in humans. Prior group review is sufficent to deliberate the harms and benefits. No national consensus-testing is required for experimental human gene therapy for single-gene disorders.

Even if successful animal genetic experiments met the criteria described above, there would still be an unknown to be crossed. Are human genetics sufficiently different from animal genetics to distrust a scientific standard that approximated perfection in animal experiments? Scientific assertions and facts could doubtless be advanced to answer the question, but nontheless doubt will remain until gene therapy in humans was done with no harmful effects in subjects or offspring. The first generation of experimental subjects for gene therapy will probably be children, infants and perhaps fetuses of parents at risk for recessive genetic disorders. The therapy will be attempted rarely at first, the better to study the results. Only if evidence accumulated over many years showed that single-gene corrections did not interact harmfully with polygenic arrangements necessary for higher functions like memory, intelligence, fertility, and emotional characteristics would it then be ethical to construe human gene therapy as "standard practice."

Ought the risk to be taken in the first place with gene therapy? My argument above would support such risk-taking, if in the best judgment of those most directly concerned, with the voluntary consent of the parents, the experiment were considered worthwhile. In the absence of any scientific evidence to the contrary, I hold that we ought to be ready to act on the good ethical reasons why gene therapy is acceptable. We should not regard gene therapy in a different category because it is directed towards genes rather than other targets. It may turn out that the genetic defects of higher animals and humans are easier to modify than was once believed. If so, several strong ethical reasons exist to incorporate genetic measures into the history of medicine. I see no rational reason to accord the locations of human DNA that encode messages that directly harm humans more or less respect than we ought to give any other aspect of human physical and mental existence. Above all, we ought not to be afraid, given animal evidence, to take the first step into the next unknown, simply because human genes become objects of deliberate change.

Ethical Issues and Gametic Correction

In retrospect, Nirenberg's ethical appeal is more relevant today to the prospect of correction of gametic, rather than somatic, cells. Scientists will possibly learn how to alter human sex cells long before there will be sufficient wisdom (ethical content) to guide the use of this knowledge for the benefit of humankind.

Why would it be necessary to learn to alter gametic cells? Let us look ahead 50 to 100 years. Let us presume that gene therapy had been very successful in a generation of children and young persons affected by single gene disorders. Further, presume that the benefits of post-natal gene therapy were effective for the patient but not for his or her children because the basic genetic information originally transmitted by the gametes had not been altered. More carriers would live longer, disease-free lives, but their more numerous children would still be at risk. Presume further that animal experiments had shown that DNA insertions in the animal embryo not only corrected the disease in the eventual parent but in its offspring for several generations.

In such a future, there would be a need, related to the prospect of treating a genetic disorder at it source, for (1) study of the development of the zygote to learn how genetic disorders begin and function, and (2) eventual trials of gene therapy in the context of fertilization to find if correction of cells at the earliest stage of development prevents the disorder by inheritance of the correction in children and in subsequent generations.

I define the zygote as the product of human fertilization before the completion of the process of implantation, usually a period of from 12-14 days following fertilization. At this earliest stage of development, it is not yet clear if the fusion cell or zygote will divide further to become more than one. A human embryo stage follows upon implantation; a fetal stage could be said to begin at about the sixth week of gestation. (Grobstein, p.87)

In approaching the question of whether it would ever be ethically acceptable to deliberately modify human gametes, a prior question should be raised about the ethics of zygote experiments. The most extensive inquiry to date on this issue was conducted by the Ethics Advisory Board (EAB) of the Department of Health, Education, and Welfare. The EAB's recommendations and report were published in 1979.[48] The question of pre-implantation experiments was not the central issue explored by the EAB. They studied the ethical and scientific arguments for and against research designed to study *in vitro* fertilization (IVF) and subsequent transfer of the newly fertilized zygote to the human uterus. To review the full question, the EAB had to subdivide research on IVF alone and transfer alone. Some research would be proposed to study IVF with no intent to transfer the zygote after the research, but to study the condition of the zygote after IVF and prior to future attempts to transfer. The EAB had to face the question of whether it would be ethical to study the human zygote under circumstances in which it would not survive.

The EAB recommended approving this type of research with the following conditions:

- the research complies with all regulations governing research with human subjects (45 CFR 46)
- the research is designed primarily: (a) to establish the safety and efficacy of transfer after IVF and (b) to obtain important scientific information toward that end not reasonably attainable by other means;
- gametes used in such research should be obtained from informed and voluntarily consenting persons
- no embryos should be sustained *in vitro* beyond the stage normally associated with the completion of fertilization (14 days after fertilization); and
- prompt reporting of evidence of risks of abnormal offspring higher than those associated with natural human reproduction.

The key assumptions in these recommendations are: (1) the purpose of the study has to be related to the safety of embryo transfer, a process positively related to the survival of future embryos and the relief of the suffering of infertility; (2) the scientific merit of the study must be exceptional and singularly attainable only in the human zygotes, (3) informed consent is required, and (4) the moral status of the zygote to be studied is respected through the restrictions and care imposed by the review process, but is not to be considered equal to that of a human fetus.

Assuming real success in animal experiments with genetic disorders, the same reasoning could be used to support study of donated human gametes and subsequent zygotes from couples at risk for single-gene disorders whose children will suffer more unless successful therapies are discovered. Studies of the processes by which gene action begins in these conditions will undoubtedly shed light on the most effective methods to deliver gene therapy at subsequent stages of life. Ethically considered, there is an even more weighty reason to study the gametes and zygotes of couples at risk for recessive disorders, because the actual burden of suffering is greater on them than the burden of infertility, although I acknowledge that real suffering is caused by involuntary infertility. I see no significant morally relevant differences between the Board's reasoning on IVF and transfer and future reasoning to study zygotes to gain better understanding of the onset of genetic disorders. I raise the following questions for discussion and debate in relation to research with human embryos:

(1) Is the reasoning of the EAB about study of the fertilized zygote after IVF with no intention for transfer ethically acceptable?

(2) If so, then if modes of effective gene therapy had already been proven in animals why would it not be acceptable to study gene action in zygotes that are homozygous or heterozygous for human genetic disorders?

If sufficient study of human embryos is accomplished to develop a theory and methods to attempt gametic correction in the process of fertilization, the knowledge prophesied by Nirenberg would be available. But should it be done? Would it ever be ethical to attempt to correct genetic disorders by genetic modification of gametes or the blastocyst in the earliest stage? Grobstein described the scientific possibilities opened by external fertilization:

> The inner cell mass of the blastocyst is the precursor to all cells of the embryo proper. If the genetic constitution of a significant number of its cells were suitably changed, so, too, might be that of the germinal cells that give rise to sperm and eggs. (p.124)

He called for much more work in animals (mice) to this end, but in the event of success, he commented that motivation would be strong to attempt the procedure in humans, especially whose offspring suffer from recessive genetic disorders.

Arguments Against Gametic Correction in the Human Embryo

More recently, Bayles[49] and Williamson[50] argued that, in the present context of science and medicine, it would be irrational and unethical to attempt gametic correction in the human embryo as a means of avoidance of a genetic disorder. Their concern reflects primarily the danger of mutagenic harm. To cite Bayles:

> Rational persons would not approve of attempts at genetic modification, even to correct defects. In comparison to the alternatives, such modification is not worth trying. If a defect is discovered in an embryo, an alternative to attempting modification is simply not implanting it. Attempts at modification might or might not be successful and risk introducing other defects. Rational persons would prefer destruction of the embryo and creating another one for implantation. The choice is between a risk of a significant defect with this embryo and using another embryo without such a risk. As rational persons would not accord embryos moral status and would accept the principle of risk to the unborn, they would find such attempts at genetic modification to be ethically wrong

By Bayles' principle of "risk to the unborn" he means that it is wrong to incur a real risk that an unborn child will have a genetic disorder or handicap. By this principle, parents who knowingly risk the transmission of a defect are to be morally condemned, and pregnant women who risk damage to the fetus, including genetic modification, are also to be condemned. Bayles clearly prefers abortion as a long-term, even permanent solution to genetic disorders, to the risk of more genetic mistakes through manipulation.

Bayles' argument is further premised on the assumption that it is irrational to want genetic offspring. One ought, in his view, simply be satisfied with having a child to rear but not "irrationally" demand genetic continuity. I fail to understand why it is irrational to desire genetic offspring. The biologically-based desire to reproduce is a fact about human nature and necessary for human evolution. Some genetic continuity is even necessary for human ethical systems to evolve and survive. It may be irrational for many reasons to act on the desire, especially if one is at risk for a serious genetic disorder. But it is hardly irrational to want to continue aspects of one's genotype with the certain knowledge that it will not remain the same.

Bayles' readiness to condemn some parents who take the risk of reproduction is understandable if one accepts his central premises about the ethics of reproduction. Biologically-based desires and loyalities count for very little in his view. Reason counts for almost everything. But how can reason be separated so sharply from the physical basis of reason? In my view, his ethics are perfectionistic and fall too heavily on a visible few in a genetic world which everyone is at risk. Some suffer more visibly because of the accidents of biological and cultural evolution, but all are accident prone. Before condemning persons who risk reproduction Bayles should first examine whether he is short-sighted about the possibility of preventing the cause of specific disorders *safely*, rather than assume the worst. His caution about the danger of genetic defects due to modification certainly fits the state of current knowledge, but will it always fit in the future? Would it not be rational to prevent genetic some disorders within ethical limits? What if some gametic modification of the cause of genetic disorders could eventually be done *without* harmful mutations? A philosophy based on rational thought is open to evidence. Later generations of scientists building on gene therapy in animals and humans may find that it is easy to correct for a few single-gene defects at their source, but impossible to carry out polygenic modificatons by genetic measures for more complex disorders. Then, might it be ethical to attempt to prevent some genetic disorders?

I offer the following as examples for debate and discussion:

- If certain X-linked disorders (e.g. Lesch Nyhan syndrome, hemophilia, etc.) might be approached through modification of the female X-chromosome during fetal development, the result could be avoidance of sex selection by abortion or sex determination, emancipation of female carriers from the stigma of their biological role, and ideally, prevention of the disease.
- If it were safe to correct the sperm in male heterozygotes in a male-female pair of carriers, there would be a zero chance of their children having the recessive disorder in their lifetime.
- In a dominant disorder (e.g. Huntington's disease) with a 50 percent risk each child will be affected, if the gametes of each zygote could be corrected in the context of external fertilization, the disorder could eventually be prevented.

My aims are to prevent the disorder and to provide the fulfilment of having a healthy child. Do these aims overstress the human desire for childbearing and suggest an unlimited right to have a child? No single value, ideal, or biological tendency should be absolutized, including the function of human reproduction. But if it were possible to effect such changes without inheritable harmful effects, why should we withhold the ability? Imagine a dialogue with the affected offspring of such couples in generations to come. If asked why we withheld knowledge to correct genetic disorders, and we answered "We thought it would eventually be more injurious to society," the appropriate response of the future affected person would be "What did you do to learn whether it would or would not be injurious?"

Other Ethical and Metaphysical Arguments Against Gametic Correction

In the early 1970's Kass[51] and Ramsey [52] mounted strong arguments against *in vitro* fertilization on the ground that experimentation with human zygotes or embryos might provide opportunities to correct genetic defects at their source in the gametes. These critics, a physician-philosopher, and an ethicist, warned of the gravest ethical dangers proceeding from gametic modifications. They foresaw not only *physical* and genetic consequences such as:

- unforeseeable genetic dislocation and damage to future generations,

but *social* harms, such as:

- misadventurous experimentation, without consent, on the well-being of individuals yet to be born
- the likelihood that zygotes would be grown under laboratory conditions for into the embryo stage, and manipulated in experiments, with resultant dehumanization of the scientists and society
- The use of positive eugenics and genetic engineering to attempt to "improve" complex traits like intelligence, memory, life-span, etc.

and finally, harms that can only be described as metaphysical, so total in their impact that human life and existing ethical systems would become unrecognizable.

For example, Kass wrote:

> "The 'New Beginnings in Life' may be the 'transition to a wholly new path of evolution.' It may, therefore, mark the end of human life as we and all other humans have known it. It is possible that the non-human life which may take our place will be superior, but I think it most unlikely and certainly not demonstrable. In either case, we are ourselves human beings; therefore, we have a proprietary interest in our survival, and our survival as human beings. (p. 61)

And Ramsey, writing in the same volume about the progressively harmful consequences of genetic knowledge:

> Before us then opens up the dizzy, abysmal prospect that men can be present where the foundations of the world were laid. Piece by piece of information may destroy our sense, that for all the genetic corruption, God made the world and the human creature and they are good. We may finally lose our faith that, under God, life should always be affirmed with joy and hope beyond despair - and lose also our concern that even genetically defective lives be saved and cared for. (p.175)

Their judgments, written in 1972, have not come to pass but they should be taken seriously in debating the future of applied human genetics. In my view, these consequences are highly unlikely in a pluralostic, democratic society that strongly guides the use of genetic knowledge towards therapeutic aims. Kass' and Ramsey's initial concerns about harmful physical genetic consequences due to DNA insertions can be answered first by experiments in mice and gradually in higher species. If experiments fail, neither gene therapy nor gametic correction in humans should have a future.

Harmful social consequences (unethical experiments, ectogenesis, and polygenic genetic engineering) could be prevented by continuous monitoring of the disciplines that employ genetic knowledge or recombinant DNA technology and the use of existing (or strengthened) social controls on science and scientists. Legal measures should only be used to correct or remedy real abuses or harms, but legislatures and courts are additional means of prevention.

Two ways to respond to perceived threats to human values and ethical systems due to genetic interventions are available. First, there is an empirical side to the issue which can be investigated and studied. Human ethical systems have evolved in the context of biological and cultural evolution. What is the role of animal and human genetics in the development of ethical systems? What is the weight of biological evolution in cultural evolution? The interest of sociobiologists[53,54] and philosophers [55,56] in the evolution of altruism and other ethical systems in human populations is rapidly producing a large and interesting literature that shows the importance of a physical substructure for human evolution mediated by genes. Human physical constitution makes possible and interacts with human culture to produce the species with the most open future. What are the possible effects on ethical systems of deliberate medical-genetic intervention?

The other way to meet metaphysical challenges is by an argument on the same level. I have argued above only for genetic intervention to treat or prevent well-defined monogenic disorders that cause great human suffering. Could we radically alter our own or other's human nature by treating genetic disorders, albeit by genetic measures? In my view, we would continue to recognize ourselves as companions in a historical process of healing and emancipation from burdens that have biological and cultural, rather than supernatural, origins. The benefits of genetic methods to treat and prevent genetic disorders could be gradually and safely mediated to society through the self-understanding of persons like ourselves and within the ethical systems we know and help to maintain. If these events came to pass, however, we would not remain entirely the same, to be sure, in an ethical or metaphysical sense. A new power would have been added to human culture that would require the utmost scrutiny and caution to control. The sphere of human freedom would have been vastly expanded, but new limits would also be imposed by those who followed those who first used genetic therapies.

Would those who were treated by genetic measures perceive that they were qualitatively different than other human beings? Would persons born in another generation free of a genetic disorder and the fear of transmitting it feel violated as humans? If these persons share similar ethical traditions as we respect, my vision is that they would be grateful and relieved when they learned the whole story.

The metaphysical meaning of the medical genetics that I foresee is the giving and receiving of help between companions in the struggle to survive, grow, and fulfill oneself as a person in the community of persons. The oldest and the newest forms of wisdom will keep applied human genetics on a firm course of medically relevant aims. To stray off that course may indeed risk harm to basic ethical systems and the freedom that sustains the concept of personhood treasured by our society.

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Mr. GORE. Thank you very much. We will hold questions until the entire panel has completed their presentations.

Dr. LeRoy Walters, director, Center for Bioethics, Kennedy Institute of Ethics, Georgetown University. Welcome and please proceed.

Dr. WALTERS. Thank you, Mr. Chairman.

Mr. Chairman and members of the committee and subcommittee, gene therapy raises two types of questions which are quite distinct. The first is a rather conventional and traditional question: What kinds of treatment should we accept for ourselves or our children? The second is a novel question for the human race: What kinds of genetic inheritance should we pass on to our descendants in the third and fourth generations, and beyond? I will discuss these questions primarily as they relate to the cure of clearly identifiable genetic diseases. However, I will conclude by exploring how these two questions relate to a future, hypothetical possibility—that we may one day possess the ability not only to cure genetic diseases, but also to enhance human capabilities by genetic means.

I. THE CORRECTION OF HUMAN GENETIC DEFECTS

The primary ethical rationale for attempting to correct human genetic defects by means of gene therapy is a simple consequentialist argument. There is a group of genetic diseases which have proven to be intractible to currently available methods of health care.

The earliest targets for gene therapy will probably be defects involving only a single gene—for example, cystic fibrosis, sickle-cell anemia, Duchenne muscular dystrophy, and some types of thalassemia. For all of these diseases only palliative care can be given; the disease process itself cannot be reversed.

The single-gene defects exact an enormous toll of human suffering. According to a recent World Health Organization report, approximately 200,000 children die each year from the effects of inherited blood disorders like sickle-cell anemia and thalassemia. That is 200,000 children in the world. In Great Britain almost one percent of all children are afflicted by serious single-gene defects, especially cystic fibrosis, muscular dystrophy, and hemophilia. Similar figures obtain for the United States.

The specific type of gene therapy for which the ethical rationale seems strongest is somatic-cell, or nonreproductive cell, modification for a consenting adult suffering from a debilitating or lethal single-gene defect. We might call this type of gene therapy the simplest paradigm case because it involves all the factors most likely to justify gene therapy from a moral point of view: a life-threatening illness; a relatively uncomplicated genetic defect; a patient capable of consent; and no transmission of the genetic change to future generations.

The primary ethical argument against gene therapy, even in the simplest paradigm case, is that such intervention would be the first step toward the genetic engineering of human beings or toward the human control of evolution. This first-step counterargument is also consequentialist in character. In order to assess its validity, we would first need more precise definitions of genetic engineering and human control of evolution. With these more precise definitions in hand, we could then calmly compare the probability and magnitude of benefit from gene therapy with the probability and magnitude of harm likely to result from the application of this technique. My conclusion is that, at least in the simplest paradigm case, the potential benefits of gene therapy to patients suffering from serious genetic disease far exceed the potential harms of gene therapy to the human race.

As we move away from the simplest paradigm case, with the consenting adult, to other cases, the burden of moral justification becomes greater. For example, parents may one day face the question of consenting to the genetic modification of somatic cells not for themselves but for their children. Indeed, there may be good clinical reasons for performing gene therapy for some genetic diseases in infancy—before the immune rejection system has matured and before the disease has seriously damaged the victim's body. However, from an ethical point of view, proxy decisions made on behalf of another are always more complicated than decisions made by adults on their own behalf. Thus, parents considering gene therapy by somatic-cell modification for their children should, at a minimum, carefully assess whether they would be willing to accept the same treatment for themselves.

Even more momentous than decisions about somatic changes in our children will be deliberations about whether to transmit the correction of genetic defects to multiple future generations. Recent laboratory research with animals suggests that such changes may one day be technically feasible in humans either through the repair of sperm and egg cells before fertilization begins or through the microinjection of genetic material into the very early human embryo. In either case the genetic correction would affect both the somatic and the reproductive or germ cells of the offspring and would be passed on to subsequent generations through the germ cells, the offspring's sperm or ova.

The major ethical arguments against germ cell modification for the correction of human genetics defects are:

First, that the same technique could be misused for destructive purposes; and

Second, that we lack the wisdom to know what type of genetic endowment our far-off descendants would want to have.

The history of medicine or of technology more generally reveals quite clearly that the potential for misuse is always present. Again, a careful assessment of potential benefits and harms will be required. However, in my view social and political safeguards against the potential misuse of germ-cell modification can be established which will allow for the constructive use of this powerful technique.

As for the argument that we lack the wisdom to decide for distant generations, there are some cases in which we can be quite sure about what our descendants in the coming generations will want. The eradication of single-gene defects from the human gene pool seems an eminently worthy goal, at least as worthy as global efforts to eliminate smallpox or measles. If we are concerned that future generations may need the genes that cause single-gene defects in order to survive in novel circumstances, then let us preserve such genes in repositories—as the smallpox virus is preserved—rather than in people.

In my prepared written statement I go on at this point to discuss the actions of the Parliamentary Assembly of the Council of Europe. In January of this year that body adopted a recommendation approving the use of germ cell modification for serious genetic disease. In that connection the Parliamentary Assembly proposed the construction of a list of diseases that would be particularly appropriate targets for gene therapy both by somatic cell modification and by germ cell modification.

II. THE ENHANCEMENT OF HUMAN CAPABILITIES

I turn then to a more controversial topic, the enhancement of human capabilities. Highly respected scientists have seriously questioned the technical feasibility of ever enhancing human capabilities, especially behavioral traits, by means of gene therapy. For example, in a much cited article published in Science in 1970, Professor Bernard Davis argued that single gene defects like the one that causes sickle-cell anemia may ultimately be reparable, able to be repaired, but that human behavioral traits are polygenically based and thus probably not amenable to modification by genetic means.

Recognizing these theoretical difficulties facing attempts to enhance human capabilities by means of gene therapy, let us imagine for a moment that in the year 2050 the unlikely has become feasible and that well characterized alterations at the sites of 15 known genes have been demonstrated to double the efficiency of human long-term memory. Would the use of gene therapy for the improvement of long-term memory be morally justifiable?

This thought-experiment reveals something quite interesting about the notions of positive and negative eugenics and about our concepts of health and disease. Many human characteristics can be described as deficits in the light of goals not yet attained. Thus, forgetfulness can easily be categorized as a deficit, and the remedying of forgetfulness can be construed as an exercise in negative eugenics, if one wishes to use the term "eugencics."

Similarly, when we speak of diseases which might be treated by means of gene therapy, we normally think of specific physical problems, like those resulting from the improper function of the gene that codes for beta-globin, which in turn leads to certain types of thalassemia. However, if certain psychological deficits are also included in the concept of disease, then forgetfulness may be a candidate for therapy as well. The enhancement of human long-term memory efficiency by genetic means would be least problematic from a moral point of view, if an adult chose such alteration only for himself or herself. Presumably the memory enhancement would be accomplished through precise, well understood modifications in the appropriate cells of the brain. Somewhat more complicated would be cases in which parents wanted to enhance the memory capacities of their children through the genetic modification of somatic cells. One can easily envision potential abuses, for example, competitive excesses by over-zealous parents, that would require timely ethical scrutiny and perhaps even formal social control. On the other hand, the judicious, voluntary use of genetic memory enhancement techniques in children, if the techniques were demonstrated to be safe and effective, could conceivably contribute to an enriched educational experience and an improved quality of life for members of the next generation. If successful, these memory enhancement techniques might effect a change in one human mental capacity analogous to the changes wrought in the external world by microcomputers.

With the hypothetical case of somatic cell modification for memory enhancement in children, we are but one step removed from the most difficult paradigm case, the proposal to transmit such memory enhancement to multiple future generations through germ cell modification. The most difficult paradigm case is the polar opposite of the simplest paradigm case and would include the following elements: a psychological deficit, for example, forgetfulness; a relatively complicated, polygenic basis for the deficit; a decision affecting potential people who would be unable to consent or refuse; and transmission of the genetic change through the germ line to future generations.

Here we reach an outer limit of both technical and ethical imagination. One is rendered almost speechless even contemplating the possibility that enhancements of human capabilities might one day be able to be transmitted to our progeny. Yet if certain enhancements by means of somatic cell modification prove to be highly beneficial to members of a particular generation, then some or many or perhaps even most members of that generation may justifiably decide to bequeath the enhanced capability through the germ line to even their distant descendants.

My general conclusion is a quite simple one: We should not foreclose in principle any potentially constructive application of gene therapy to human beings. The mere fact that a remotely possible technological development would force new and difficult decisions upon us should not, by itself, cause us to reject that development. Rather, it should stimulate us to reflect carefully, and well in advance, as we envision alternative human futures.

Mr. GORE. Thank you very much for a very thoughtful statement.

[The prepared statement of Mr. Walters follows:]

STATEMENT OF LEROY WALTERS, DIRECTOR, CENTER FOR BIOETHICS, KENNEDY INSTITUTE OF ETHICS, GEORGETOWN UNIVERSITY

My remarks presuppose that initial applications of gene therapy to human beings will be technically feasible within the next ten years and that during the next fifty years scientists will succeed in precisely mapping many critical regions of the human genome. My task is to attempt an anticipatory analysis of the ethical issues we will face when various modes of gene therapy are available for possible use with humans. I will present a general ethical perspective on gene therapy as a therapy. Thus, I will not discuss research issues like the type and number of animal studies to be performed before human clinical trials of gene therapy are initiated or the moral rules which should be adhered to in those clinical trials.

Gene therapy raises two types of questions which are quite distinct. The first is a rather conventional and traditional question: What kinds of treatment should we accept for ourselves or our children? The second is a novel question for the human race: What kinds of genetic inheritance should we pass on to our descendants in the third and fourth generations—and beyond? I will discuss these questions primarily as they relate to clearly-identifiable genetic diseases. However, I will conclude by exploring how these two questions relate to a future, hypothetical possibility—that we may one day possess the ability not only to cure genetic diseases but also to enhance human capabilities by genetic means.

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The single-gene defects exact an enormous toll of human suffering. According to a recent World Health Organization report, approximately 200,000 children die each year from the effects of inherited blood disorders like sickle-cell anemia and thalassemia. In Great Britain, almost 1 percent of all children are afflicted by serious single-gene defects,[1] especially cystic fibrosis, muscular dystrophy, and hemophilia.[2] Similar figures obtain for the United States.[3]

The specific type of gene therapy for which the ethical rationale seems strongest is somatic-cell (or non-reproductive-cell) modification for a consenting adult suffering from a debilitating or lethal single-gene defect. We might call this type of gene therapy the Simplest Paradigm Case because it involves all the factors most likely to justify gene therapy from a moral point of view: a life-threatening illness; a relatively uncomplicated genetic defect; a patient capable of consent; no transmission of the genetic change to future generations.

The primary ethical argument against gene therapy, even in the Simplest Paradigm Case, is that such intervention would be the first step toward the genetic engineering of human beings or toward the human control of evolution. This first-step counterargument is also consequentialist in character. In order to assess its validity, we would first need more precise definitions of "genetic engineering" and "human control of evolution." With these more precise definitions in hand we could then calmly compare the probability and magnitude of benefit from gene therapy with the probability and magnitude of harm likely to result from the application of this technique. My conclusion is that, at least in the Simplest Paradigm Case, the potential benefits of gene therapy to patients suffering from serious genetic disease far exceed the potential harms of gene therapy to the human race.

As we move away from the Simplest Paradigm Case to other cases the burden of moral justification becomes greater. For example, parents may one day face the question of consenting to the genetic modification of somatic cells not for themselves but for their children. Indeed, there may be good clinical reasons for performing gene therapy for some genetic diseases in infancy—before the immune rejection system has matured and before the disease has seriously damaged the victim's body.[4] However, from an ethical point of view, proxy decisions made on behalf of another are always more complicated than decisions made by adults on their own behalf. Thus, parents considering gene therapy by somatic-cell modification for their children should, at a minimum, carefully assess whether they would be willing to accept the same treatment for themselves.

Even more momentous than decisions about somatic changes in our children will be deliberations about whether to transmit the correction of genetic defects to multiple future generations. Recent laboratory research with animals suggests that such changes may one day be technically feasible in humans either through the repair of sperm and egg cells before fertilization begins or through the microinjection of genetic material into the very early human embryo.[5] In either case the genetic correction would affect both the somatic and the reproductive or germ cells of the offspring and would be passed on to subsequent generations through the germ cells, the offspring's sperm or ova.

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[1] Williamson B. Gene therapy. *Nature*. July 29, 1982: 298 (5873); 417. Cf. Ruddle F. A new era in mammalian gene mapping: somatic cell genetics and recombinant DNA methodologies. *Nature*. Nov. 12, 1981: 294(5827); 115–120.

[2] Williamson B, *op. cit.*, p. 416.

[3] Lubs HA. Frequency of genetic disease. In: Lubs HA; de la Cruz F; eds. Genetic counseling: a monograph of the National Institute of Child Health and Human Development (New York: Raven Press, 1977): 5–9.

[4] Williamson B, *op. cit.*, p.417.

[5] Palmiter RD; Chen HY; Brinster RL. Differential regulation of metallothionein-thymidine kinase fusion genes in transgenic mice and their offspring. Cell. June 1982: 29(2); 701–710.

The major ethical arguments against germ-cell modification for the correction of human genetic defects are: 1. That the same technique could be misused for destructive purposes; and 2. That we lack the wisdom to know what type of genetic endowment our far-off descendants would want to have.

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The legislative body which seems to have given the most detailed consideration to gene therapy is the Parliamentary Assembly of the Council of Europe. In January of 1982 that body adopted a recommendation approving the use of germ-cell modification for serious genetic disease.[6] A background memorandum which the Assembly used in reaching its decision envisioned the construction of "a list of serious, malignant, inherited illnesses which we would like to see engineered away if ever possible."[7] The memorandum conceded that the construction of such a list of unwanted diseases would require extensive consultation and great tact: "It would of course be a difficult and extremely delicate affair to establish such a list. All forces from the different branches of society would have to join. It ought to be done internationally and with full governmental, parliamentary and public backing. The list would have to be updated from time to time, but some principles should be absolute and always have to be followed categorically, for example, that race or sex could never be listed as such illnesses."[8]

Whatever one's evaluation of the specific implementation plan envisioned by the Parliamentary Assembly, it is significant that this international body, in the midst of proclaiming the human right to "a genetic inheritance which has not been artificially interfered with," [9] explicitly approved germ-cell modification for the cure and prevention of serious genetic diseases.

II. THE ENHANCEMENT OF HUMAN CAPABILITIES

I turn now from the use of gene therapy to correct specific defects to the employment of genetic techniques to enhance human capabilities. This question has often been addressed as the problem of positive eugenics, although there is no necessary link between genetic enhancement and social programs of eugenics.

Highly-respected scientists have seriously questioned the technical feasibility of ever enhancing human capabilities, especially behavioral traits, by means of gene therapy. For example, in a much-cited article published in Science in 1970, Professor Bernard Davis argued that single-gene defects like the one that causes sickle-cell anemia may ultimately be reparable but that human behavioral traits are polygenically based and thus probably not amenable to modification by genetic means.[10]

Recognizing these theoretical difficulties facing attempts to enhance human capabilities by means of gene therapy, let us imagine for a moment that in the year 2050 the unlikely has become feasible and that well-characterized alterations at the sites of fifteen known genes have been demonstrated to double the efficiency of human long-term memory. Would the use of gene therapy for the improvement of long-term memory be morally justifiable?

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[6] Council of Europe, Parliamentary Assembly, Thirty-Third Ordinary Session (Third Part), Jan. 25-29, 1982. Recommendation 934 (1982) on genetic engineering. In: Texts adopted by the Assembly (Strasbourg: Council of Europe, 1982): 2-3.

[7] Council of Europe, Parliamentary Assembly, Thirty-Third Ordinary Session (Third Part), Jan. 25-29, 1982. Document 4832: Report on genetic engineering. In Documents: working papers (Strasbourg: Council of Europe, 1982): 16.

[8] *Ibid.*

[9] Council of Europe, Recommendation 934, Texts adopted by the Assembly, *op. cit.*, p. 3.

[10] Davis BD. Prospects for genetic engineering in man. *Science.* Dec. 18, 1970, 170(3964); 1280.

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My general conclusion is a quite simple one: We should not foreclose in principle any potentially constructive application of gene therapy to human beings. The mere fact that a remotely-possible technological development would force new and difficult decisions upon us should not, by itself, cause us to reject that development. Rather, it should stimulate us to reflect carefully, and well in advance, as we envision alternative human futures.

Mr. GORE. Now I would like to call on Dr. Richard Zaner, professor of medical ethics, at Vanderbilt University School of Medicine, and I would like to also welcome you as a fellow Tennessean, Dr. Zaner.

Dr. ZANER. Thank you, Mr. Chairman.

I am delighted to be here and appreciate the invitation. I have already gone on public record, as you probably know, as being convinced that the issues central to this hearing are, so far as I can tell, among the most significant we as a society will face in the foreseeable future, and on record as in support of some of these technologies, as I have worked with some of the researchers at Vanderbilt on many of them.

It has been, of course, commonplace for some time to note that modern technologies affect human society, and natural environments in significant, complex and subtle ways.

It has by now also become commonplace to stress that the newest form of modern technology—genetic engineering—is quite unique, acting directly on human beings themselves.

In Leon Kass' more colorful terms, for the first time "man can recreate himself."

All this clearly makes necessary an equally awesome wisdom, one which, however, we do not seem to possess, and which many of us today have ceased to believe is even possible.

At least three things in this context seem to me necessary:

No. 1, to understand not merely individual technologies, which I regard as terribly important, but the kind of power now in principle possible; what is plausible now to contemplate.

No. 2, to understand clearly what responsibilities and obligations and accountabilities have therefore become requisite.

No. 3, to develop at least the minimum of a framework or foundation for the moral discernment, discussion and assessment of these powers. I will try to say something helpful on each of these.

First, the very commonplace nature of so much of our technological achievements harbors problems: We may too quickly tend to ignore them, take them for granted, as our space flights have been taken for granted very quickly. Doing this, we may also easily forget that the very abstractness of our language can befuddle us: for example, to talk of man's power over nature may obscure the reality that it is individual people who in fact wield power over other people and populations.

My colleague, Professor Walters, has underscored the problems in the ways in which we use these terms such as deficit, disease, positive or negative as regards eugenics and so on.

In the same way, the very abstractness of our usual talk may tend to conceal the kind of power now in principle possible and the range of applications of this power.

There are basically three areas which concern me and I hope concern the rest of us.

First, our technological prowess in biomedicine and medicine has already made it plausible to think and to practice in some ways the genetic control of future humanity.

In the geneticist, Sir John Eccles' words, we can now take biological evolution into our own hands, including our own evolution.

As we have in his terms "enslaved" useful species already, so we can now do so as regards human beings.

Second, to the same extent, it is now plausible and practical already to exercise this control as regards present-day human populations and individuals.

Through psychopharmacological and behavior modification techniques, one can circumvent human speech, meaning and action, bypass choice, and go directly to work to modify the human material substrata itself.

Finally, third, understanding not only disease, pain, malnutrition and so on as genetically determined, but in the terms of the geneticist, Sir McFarlane Burnett, also war, evil and even death and dying as the result of genetic errors or genetic encodings in somatic cells, it now seems plausible to him that we can bring our own mortality within the circuit of our own control.

This power, that is, expresses the ability of the user of such technologies to alter perhaps irrevocably our very capacity to reckon with and to understand those very technologies, hence biomedicine and medicine, and ultimately ourselves.

It is a power, in other words, whose use is defined by its very capacity to cancel out all cognizance of its having been used in the first place, and thus directly affects human beings in their most intimate humanity.

My second general point is that, to mention the nature of our technological power, is neither to condemn nor to baptize it. I wish rather thereby to underscore both the urgency and the scope of the kind of wisdom and knowledge such technology brings with it, the scope of responsibility, of obligation, and accountability we face socially, morally, and politically.

Moral as well as social policy implications are clearly inherent to them. What seems needed first of all, if you will, to repeat a point made earlier by our theological friends, is a clear perception of reality. A first step has already been taken by stressing or suggesting the kind of power already in principle plausible.

Second, the very usefulness of such biomedical knowledge itself creates the need—as Hans Jonas pointed out some years ago—for a very different kind of knowledge, namely, a knowledge of ends and goals.

Without that, we shall indeed float blindly and randomly.

Such a knowledge of ends, however, is not what is often appealed to by some of our prominent researchers, scientists, and physicians.

Even while recognizing that it has often been scientists who have first blown the whistle on various abuses and misuses of technology, many of them seem to believe that their code of ethics derives from and is to be justified solely in terms of what is called a social consensus. Thus Gerald Weissman says a society "gets not only the government, but the science it deserves," and he warns us that if we do not want to have the Golem, chimeras, or the fantasies of the Andromeda strain, we had better assure that our society itself doesn't want such fantasies realized.

Will this give us the kind of knowledge of ends and goals, the sort of wisdom needed? I think not.

In the first place, such a view is blatantly relativistic, does not permit in other words any moral judgments on any society's use or abuse of such virulent technologies. It merely permits claims of differences, not of moral evil or good.

In the second place, the use of abstractions such as social consensus, society, and so on, only obscures the discomforting fact that those who know those technologies the best, or those who pay for the research and the products of it, are those who in fact can exercise the power. To appeal for moral legitimacy for such abstractions is effectively to obscure the legitimacy of power use and abuse and to give license to anybody to define these terms as suits them.

Even more, such claims as I am looking at here, that science's ethics are simply derived from the general culture, while it may indeed be true for some scientists, by no means answers the question the research poses as essential, whether science should have some special moral responsibilities and accountabilities.

I myself believe that the answer is most affirmative, and this calls for some explanation since such an answer often seems to conjure up the ugly specter of censorship to many scientists. It was, as referred to this morning, the Asilourar Conference on DNA Research, which suggests two crucial points: First, the critical absence in our culture of socially legitimated and recognized forums for the discussion and eventual settlement, hopefully, of issues raised by these new technologies, but also, second, the positive need for a code of ethics for such sciences precisely in view of their humanly potent implications and applications, otherwise existing under little or no effective controls.

Now what I am suggesting is not only that these suggestions are not censorship. To call them that is to misunderstand them most centrally. But also that we have reached the time when it is simply necessary to understand science as not in the least relieved of questions about ends, purposes, aims, and goals, nor can we any longer take it for granted that the output of science, neither its theories, its knowledge nor its many technologies, are benign.

Precisely because, in Hans Jonas' terms, the boundaries between theory and practice in science have become blurred, and the two are now fused into the very heart of science itself, the ancient alibi of pure theory, so-called value-free science, and the moral immunity it provided, no longer hold.

This implies in the words of Steven Toulmin that the professional organizations and priorities of scientific work can no longer be concerned solely with considerations of intellectual content and merit, such as "Thou shalt not fudge the data," as contrasted with the ethical and social acceptability either of the research process itself, or of its practical consequences.

In short, I am arguing, a professional moral code binding throughout, whether aided by Federal participation or not, for such scientists seems to me long overdue, very much on the model of medicine or of law. The social consequences of such science, its inherent tie with immediately realizable and realized technologies may imply precisely that the moral dimensions and responsibilities of science can no longer be ignored by scientists themselves, for the scientists themselves, it seems to me, bear the obligations to bind themselves first and foremost to such a code. That other social agencies also have legitimate responsibilities here is granted, as it is clear that considerable dialog among scientists, ethicists, theologians and the public is clearly called for on a continuous, regional, and local basis.

A third area of concern then relates directly to that kind of code and more specially to the basis for the sort of code mentioned. The need here, it seems to me, is a common one we face together and individually. Hence it demands a dialog—socially recognized through the sorts of forums I have talked about—having common aims and needing of public support.

This type of communal forum and discussion has long been a key part of science, although its focus has only rarely been on the moral dimensions of and the social consequences stemming from that community. In effect, it is an appeal for a renewal of ourselves as a moral community, just because we now face as never before the necessity to recognize our ineluctable bonds to one another and to future generations in mutual interrelationships and actions, and that morality is precisely the binding texture of that cultural, communal cloth.

A second requisite concerns the issues needing discernment, discussion and resolution. It is this, namely, that moral issues are understandable finally only within the context of their actual occurrence. Hence the positive need for us all—ethicists especially—to be deeply informed about the actualities and possibilities of technological power in our times, that is informed of each such technology in its own terms, in its own context, its own purposes, its own aims, the persons involved, those on whom impacts can be expected, the specific problems and consequences of each, et cetera.

We may perhaps not possess the wisdom for doing this needed job. Yet medicine and biomedicine have already placed us in the midst of a demanding age, one which poses the literal remaking of ourselves and our progeny. Hence such wisdom is, while perhaps unlikely, nonetheless our greatest challenge.

From the fact of our not possessing such wisdom, however, it by no means follows that we should abstain from all such technologies, as several ethicists have maintained. To be sure, we need humility, we need greater awareness of the folly of arrogance and the like. I agree: biomedical technology is not an unmixed blessing, but the abstract terms of this should not blind us to the fact that some of these technologies are indeed wonderful blessings.

I agree: caution is imperative at every stage of every technology, actual or proposed, but that is not the same as the folly of doing nothing at all and preventing others from doing.

Control does not imply externally imposed limitation on freedom of inquiry. It seems to me the only wise controls are those which stem from an internally articulated and shared system of justified values regarding ends.

What thus seems to me requisite is finding ways by which to encourage research precisely while cultivating a kind of moral stance or attitude of moderation, of control, self-control, calmness, restraint, prudence, but also wariness, that is, alertness, a attentativeness to peril, but wary, balanced by a sense of fairness, a refusal to be taken in by deception or by the agitations of hasty passion or uninformed emotion.

It also requires being ready to reassess current or suggested priorities. There may well be issues needing attention but which are obfuscated by the glamour of new technologies and which do not need such novel solutions, such as general health care, preventive measures for individuals and populations, et cetera.

These may even be more significant at the present, and certainly less costly in many ways. Nonetheless, such needs should not obscure a crucial point: the argument they provide against genetic technologies is not abstention in any sense; it only goes to reinforce the need for extraordinary caution, restraint, constant reassessment and avoidance of extremist views of all sorts.

Thus, respect for the need for self-imposed professional codes; recognition of the realities of technological power and prospects; recognition of the constraints and demands, as well as prospects of moral community and the essential place for shared dialog; immersion within the specific contexts of biomedical and medical research with an alert and wary eye for its intrinsic rationale and impact on human and animate life; and careful cultivation of the attitude or virtue of sophrosyne—these are essential but probably not the only ingredients of any morally foundational context from within which the moral issues posed by these technologies can best be addressed, and redressed, if need be.

We do not, in my view, advance either social or moral causes by curtailments on the freedom of inquiry, but freedom of inquiry is authentic solely to the extent that it is accompanied by constant and informed criticism, caution, and requirements for justification of every stage and step of each and every technology.

The requirements of such power as is now in the hands of some of us is the demand on us all to assume the equally awesome responsibiiity of gaining wisdom and maturity—individually, and as a culture, a society—to provide for the legitimate and socially recognized local forums of discussion and resolution of many of these issues outside the essentially adversarial milieu of our legal system.

Such forums will become more possible, the more the scientific community itself adopts the suggestive model of the Asilomar Conference; that is, adopts for itself clear and commanding ethical principles binding itself.

Without such individual and societal maturity I fear Weissman's otherwise innocuous phrase, "the toyshops of our technology," will return to haunt us all and we will find ourselves the playthings of our own PacManesque toys.

[The prepared statement of Dr. Zaner follows:]

Ethics and Genetic Technology: Reflections on Power

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It has been commonplace for some time to note that modern technologies affect human society, and natural environments in significant, complex and subtle ways. It has by now also become commonplace to stress that the newest form of modern technology -- genetic engineering -- is quite unique, acting directly on human beings themselves. In Leon Kass' more colorful terms: for the first time "man can recreate himself". All this clearly makes necessary an equally awesome wisdom, one which, however, we do not seem to possess, and in which many of us today have ceased to believe is even possible.

Charges and countercharges, therefore, have flown fast, and will probably continue to fly, and arguments will tend increasingly to provoke even more extreme charges. Still these help neither the understanding of the technology, its power, nor the effort to grapple morally with them. At least three things do seem to me necessary: 1) to understand not merely individual technologies, but the kind of power now in principle possible; 2) to understand clearly what responsibilities and obligations, and accountabilities have therefore become requisite; 3) to develop at least the minimum of a framework or foundation for the moral discernment, discussion and assessment of these powers. I will try to say something helpful on each of these.

1) The very commonplace nature of so much of our technological achievements harbors problems: we may too quickly tend to ignore them, take them for granted. Doing this, we may too easily forget that the very abstractness of our language can befuddle us: e.g. to talk of "Man's power over nature" obscures the reality that it is individual people who in fact wield power over other people.

Even more, the abstractness and commonplace nature of our usual talk may tend to conceal the kind of power now in principle possible, and the range of applications of this power. There are basically three areas which concern me.

a) Our technological prowess in biomedicine and medicine have already made it plausible to think, and to practice in some ways, the genetic control of future humanity. In Sir John Eccles' words: we can now take biological evolution into our own hands, including our own. As we have "enslaved" "useful species" already, so can we now do this with human beings.

b) To the same extent, it is now plausible and practical already to exercise this control as regards present-day human populations and individuals. Through psychopharmacological and behavior modification techniques, one can circumvent human speech, meaning, and action, to bypass choice, and go directly to work to modify the human material substrata itself. Through electrical stimulation of the brain for pleasure or pain, brain surgery, operant and aversive conditioning, but also through a wide and increasing range of depressive, antidepressive, hallucinogenic and "mind-expanding" drugs.

c) Finally, understanding not only disease; pain, malnutrition, etc., as genetically determined, but also war, evil, and even death as the result of genetic errors in somatic cells (as Sir Macfarlane Burnett states), it now seems plausible to many that we can bring our own mortality within the circuit of our own control.

This power, that is, expresses the ability of the users of such technologies to alter, perhaps irrevocably, our very capacity to reckon with and to understand those very technologies, thus medicine and biomedicine, and ultimately ourselves. It is a power whose use is defined by its capacity to cancel out all cognizance of its having been used, and thus directly affects human beings in their most intimate humanity.

Such power necessarily, I believe, creates the need for an equally powerful mode of wisdom. But this wisdom, as Hans Jonas remarked years ago, seems impossible for human beings in general (because we don't possess it) and for us today in particular, because so many of us today deny the very existence of such wisdom. "We need wisdom most when we believe in it least."

2) I mention the nature of our technological power neither to condemn nor to baptize it. I wish rather to underscore both the urgency and the scope of "wisdom" such technology brings with it: the scope of responsibility, obligation, and accountability we face socially and politically. But to recognize this is at the same time to recognize that few of us understand, much less have the requisite wisdom about, just that technology. Nonetheless, grapple with this we must -- for moral as well as social policy implications are clearly inherent to it.

What seems needed first of all is a "clear perception of reality" -- a first step having already been taken by stressing the kind of power already in principle possible. Second, it is the very usefulness of such biomedical knowledge which itself creates the need for a different kind of knowledge (Jonas), namely, a knowledge of ends and goals. For without that, we shall indeed float blindly and randomly.

Such a knowledge of ends is not, however, what is often appealed to by some of our prominent scientists and physicians, namely, the "social consensus" in our society. Even while recognizing that it has been scientists who have often first blown the whistle on various abuses and misuses, many of them believe that their code of ethics derives from and is solely justified by the social consensus. Thus, Gerald Weissman says: the moral code of scientists is determined more by the general culture than by any ethics specific to science; a society "gets not only the government, but the science, it deserves." If we do not want the Golem, chimaeras, or the fantasies of the Andromeda strain, he advises, we had better ensure that our society doesn't want such fantasies realized.

Will this give us the needed wisdom? I think not, and my reasons are straightforward. a) Such a view is blatant relativism, and will not permit any moral judgments on any society's uses or abuses of such virulent technologies. b) The uses of abstractions such as "social consensus", "society," and so on, only obscures the discomforting fact that those who know these technologies the best, or those who pay for the research and the products of it, are those who in fact exercise the power. To appeal for moral legitimacy to such abstractions is effectively to obscure the reality of power's use and abuse, and to give license to anybody to define these terms as suits them. c) Even more, I think that Weissman's and other scientists' claim that science's ethics are simply derived from the general culture, while it may be true for some, by no means answers the question which is so essential: should science have special moral responsibilities and accountabilities? I myself believe that the answer is most affirmative, and this calls for explanation, since such an answer so often seems to conjure up the ugly spectre of censorship to many scientists.

It was the Asilomar Conference on recombinant DNA research which suggested two key points: a) the critical absence in our culture of socially legitimated and recognized forums for the discussion and settlement of issues raised by the new technologies, b) but also the position for a code of ethics for such sciences, precisely in view of their humanly potent implications and applications -- otherwise existing under little or no effective controls.

Now, what I am suggesting is that not only are these suggestions not censorship -- to call them that is to misunderstand them most centrally -- but also that we have reached the time, past the time, when it is simply necessary to understand science as not in the least relieved of questions about ends, purposes, aims, goals. Nor can we any longer take it for granted that the output of science -- neither its theories, its knowledge, nor its many technologies -- are benign. That is, in different terms, precisely because (Jonas) "the boundaries between theory and practice in science have become blurred, and the two are now fused into the very heart of science itself, the ancient alibi of pure theory (value-free science), and the moral immunity it provided, no longer hold."

This implies, among other things, that science, and especially biomedical science, is now to be understood as a profession in very much the same sense as either law or medicine, but especially the latter since so much of biomedicine feeds directly into medicine. (Toulmin): "the professional organization and priorities of scientific work can no longer be concerned solely with considerations of intellectual content and merit (thou shall not fudge the data), as contrasted with the ethical and social acceptability, either of the research process itself, or of its practical consequences."

In short, a moral code, binding throughout, for such scientists seems to me long over-due. The social consequences of it, its inherent tie with immediately realizable and realized technologies, imply precisely that the moral dimensions and responsibilities of science can no longer be ignored, by scientists themselves. My point: those persons who best know what goes on within science, who most closely identify with its values and aims, and who are most able to appreciate the direct technological consequences of their knowledge -- the scientists themselves -- bear the obligations to bind themselves first and foremost to a moral code. That other social agencies also have legitimate responsiblities here is granted.

3) A third area of concern relates directly to the kind of code, and more especially to the basis for that kind of code mentioned. Realizing that few of us singly have the wits or the wisdom to provide this immensely difficult program, I believe that each of us who can, must make the effort. My own contribution is merely that, and probably too modest.

a) The need here is a common one we all face together and individually; hence it demands collective dialogue having common aims and needing public support. This type of communal forum and discussion has long been a key part of science, although its focus has only rarely been on the moral dimensions of, the social consequences stemming from, that community. In effect, this shared dialogue is an appeal for a renewal of ourselves as a moral community, just because we now face as never before the necessity to recognize our ineluctable bonds to one another in mutual interrelationships and actions -- and that morality is precisely the binding texture of that cultural, communal cloth.

b) A second requisite has to do with the issues needing discernment, discussion and resolution. It is this, that moral issues are understandable finally only within the contexts of their actual occurrence. Hence, the positive need for us all, ethicists especially, to be deeply informed about the actualities and possibilities of technological power in our times -- i.e. informed of each such technology in its own terms and in its own context: its own purposes, the persons involved, those on whom impacts can be expected, the specific problems, and the consequences of each. Not every technology is like others in these respects, hence not every one stands in need of the same types of social control as do others. Here, too, talking in the abstract of "all technologies," can only result in greater confusion and harm.

c) We may not possess the wisdom for doing this needed job; yet, medicine and biomedicine have already placed us in the midst of a demanding age, one which bodes the literal remaking of ourselves and our progeny. Hence, such wisdom is, while unlikely, perhaps, nonetheless our greatest challenge.

From the fact of our not possessing such wisdom, however, it by no means follows that we should abstain from all such technologies (as several ethicists have argued). To be sure, we need humility, we need greater awareness of the folly of arrogance, and the like; but a lack of sufficient wisdom implies, not abstention, but rather great caution.

I agree: biomedical technology is not an unmixed blessing; but the abstract terms of this should not blind us to the fact that some of these technologies are indeed wonderful blessings. I agree: caution is imperative, at every stage of every technology, actual and proposed. But that is not the same as the folly of doing nothing at all, and preventing others from doing. Control does not imply externally imposed limitations on our freedom of inquiry. The only wise controls are those which stem from an internally articulated and shared system of justified values regarding ends.

What seems to me requisite is finding ways by which to encourage research while cultivating the moral stance Plato seemed to have in mind by sophrosyne -- a kind of wisdom (sophia), closely connected with justice and courage, required in the face of a lack of complete wisdom and while facing impending risks and dangers: moderation, self-control, calmness, restraint, cautions, prudence, wariness. That is, alertness, attentiveness to perils, but wary calm balanced by courage and a sense of fairness, a refusal to be taken by deception or by the agitations of hasty passion and uninformed emotion.

This complex type of virtue I believe to be positively required in our present situation. Negatively, it bespeaks resistance to hasty and premature judgment, to allowing oneself to be taken over and unbalanced by fear. Positively, it involves a readiness to act even in contexts of uncertainty and possible harms, a willingness to learn even where ambiguities beset us, a continuously present ability and readiness to say either "no" (to cease, to stop, at any point), or "yes" (to proceed, to recommence, etc.).

It also requires being ready to reassess current or suggested priorities: there may well be issues needing attention but which are obfuscated by the glamour of new technologies, and which do not need such novel solutions -- such as general health care, preventive measures for individuals and populations, etc. These may even be more significant at the present, and certainly less costly in many ways. Nonetheless, such needs should not obscure a crucial point: the argument they provide against genetic technologies is not abstention in any sense; it only goes to reinforce the need for extraordinary caution, restraint, constant reassessment, and avoidance of extremest views of all sorts.

Thus: respect for the need for self-imposed professional codes; recognition of the realities of technological power and prospects; recognition of the contraints and demands as well as prospects of moral community and the essential place for shared dialogue; immersion within the specific contexts of biomedical and medical research with an alert and wary eye for its intrinsic rationale and impact on human and animate life; and careful cultivation of the attitude or virtue of sophrosyne: these are essential, but probably not the only, ingredients of any morally foundational context from within which the moral issues posed by these technologies can best be addressed (and redressed, if need be). We do not, in my view, advance either social or moral causes by curtailments on the freedom of inquiry; but freedom of inquiry is authentic solely to the extent that it is accompanied by constant and informed criticism, caution, and requirements for justification of every stage and step of each and every technology.

The requirements of such power as is now in the hands of some of us is the demand on us all to assume the equally awesome responsibility of gaining wisdom and maturity -- individually, and as a culture, a society, to provide for the legitimate and socially recognized forums of discussion and resolution of many of these issues outside the essentially adversarial milieu of our legal system. Such forums will become more possible, the more the scientific community itself adopts the suggestive model of the Asilomar Conference, i.e. adopts for itself clear and commanding ethical principles binding itself. Without such individual and societal maturity, I fear, Weissman's otherwise innocuous phrase -- the "toyshops of our technology" -- wil return to haunt us all, and we will find ourselves the playthings of our own "Pac-manesque" toys.

Ethics and Genetic Technology: Reflections on Power

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It has been commonplace for some time to note that modern technologies affect human society and natural environments in significant, complex and subtle ways. Human, animal and vegetative forms are all affected -- at times in expected, but often in unexpected ways where our attention is alerted by damage already done. Human physical and psychic well-being, social and cultural values, lifestyles and interrelationships, are also profoundly impacted and shaped.

It has by now also become commonplace to stress that the newest form of modern technology -- genetic engineering -- is, as Mark S. Frankel noted in 1973 in his monograph, Genetic Technology: Promises and Problems[1], "unique: rather than merely acting upon man's environment, it operates directly on man himself." In this, Frankel echoed the point made earlier by Hans Jonas[2] and Leon Kass[3]. In Kass' somewhat more colorful terms, biomedical engineering, by working to change the very designer and user himself, engineers the engineer. Man can now "for the first time recreate himself," Kass emphasized in 1971, and precisely because such an awesome wisdom we on the other hand do not possess (indeed, are somewhat suspicious of), "engineering the engineer as well as the engine, we race our train we know not where."

Neither Jonas nor Kass, nor others who have expressed similar concern over the prospects of power intrinsic to the new genetic technologies,[4] I want to stress, are purveyors of the "scenarios of gloom" feared by many biomedical scientists and technologists.[5] None of the former, however, can be lightly dismissed as merely indulging their fancies by retelling the Andromeda strain fantasy, the legend of chimaeras, or the creation of the Golem -- as Gerald Weissman seems to believe,[6] in his comment on June Goodfield's summary of the "less than rational" arguments which have been so powerful in persuading public views against recombinant DNA research.[7]

To be sure, in times like these when people's passions seem so easily able to be whipped into furies, there is much plain and unsettled dust scattered willy-nilly about. In times like these, and on issues such as those which genetic technology generates, it is surely the wiser course to acknowledge that the work of most biomedical and biological researchers, and their genetic enterprise, has been largely benign to date, as Weissman says. It is also important to acknowledge that this research community has in the main embodied the "sense of humane ethics in which our society at large is impregnated."[8] In these terms, Weissman, voicing what seems clearly a widely shared belief within that research community, may seem correct: "...if we want to be sure that the scientist...does not come up with chimaeras or Golems, we'd be well-advised to make certain that our society as a whole doesn't want such fantasies realized."[9] (This point will have to be carefully looked at at a later point.)

Nonetheless, as it would be a grievous mistake to rush to hasty (and basically wrong-headed) claims about the "evils" of science and scientists, technology and technologists, so it is ill-advised (and basically wrong-headed) to take the serious and informed concerns of scholars such as Jonas, Kass and others as merely purveyors of doom and gloom and unwitted myths. For some technologies, in a word, it may be true, as Weissman says (talking of recombinant DNA research), that "the solid experimental advances of January render pointless the regulatory legislation drafted in October."[10] But this is true neither generally, of all biomedical technologies, nor always true even of those January "advances," which too often bring in their wake still other concerns.

Such extreme charges and countercharges help neither party to such disputes, nor do they advance our understanding or our efforts to grapple morally with the genuine issues which should concern us. To help us understand and struggle with them, several things are obviously necessary. First, it is imperative not merely to know what technologies have already been developed and what they have made possible, nor even what new technologies and prospects are on the immediate horizons. That is surely important; but even more important, I believe, is that we understand the kind of thing thereby opened up: not only the defacto achievements, but what has now become in principle possible. Secondly, it is imperative to understand with honesty and precision what responsibilities and obligations, as well as accountabilities, our new biomedical knowledge and technology brings with it -- whether or not our various moral and religious traditions can accommodate them. Third, it is equally imperative to meet squarely and courageously the immensely difficult, sensitive, and complex task of moral assessment: to develop a viable framework or foundation within which the costs, benefits and risks to human life and the human estate from these new technologies can be evaluated, and within which the inevitable fact of dissent and disagreement in a pluralist society can be adjudicated short of the otherwise inevitable conflict such dissent often bodes.

I will attempt to say something helpful on each of these in what follows.

II

The commonplace observation that genetic technologies are unique in operating directly on human beings -- on the users, as on the rest of us -- harbors several real dangers. Because it is so commonplace, we may tend to ignore it, subdue its actual bite. At the same time, as Kass wisely emphasized years ago, the very abstractness of our language may befuddle us: "I suspect that we prefer to speak figuratively about 'Man's power over Nature' because it obscures an unpleasant reality about human affairs. It is in fact particular men who wield power, not Man."[11] The same is true of "Science": it is not that, but particular scientists who can and do act. And, to talk of the affect on "man" by genetic technology, may well obscure the blunt and uncomfortable fact that this "power which grows is unavoidably the power of only some men, and that the number of powerful men decreases as power increases,"[12] thus leaving increased power in the hands of fewer and fewer.

Rather than addressing the assuredly very real questions of the abuse and misuse of such power, it seems to me even more important at the outset to gain a clear picture of the nature of the very power itself. To get at that, a good way seems to be a kind of indirection. The Nobel Laureate, Sir Macfarlane Burnet, noting how profoundly the whole enterprise of medicine has been changed in the last half century by biomedical technologies, wrote that as a consequence, beyond physical injury, disease, and malnutrition,

> What remains to be dealt with clinically, is almost wholly dependent on the genetic constitution of the individual and his or her response to the social environment...(W)e have to face, more critically than it has yet been looked at, the likelihood that human behavior is predominantly, and in critical matters wholly, determined at the genetic level...We may find in the end that war and evil, pain and disease, ageing and death were inevitable as soon as a working pattern of life with DNA, ATP, and protein as enzyme had been devised.[13]

Burnet's point here seems innocuous enough; despite the somewhat cool, dispassionate prose, however, even the more naive among his readers may be jarred by the idea that evil, war and even death are conceived as the results of "genetic errors in somatic cells," and indeed even "our reactions to the actualities of dying," as he goes on to maintain, "are determined by the genes we were born with to the same degree as any other aspect of our behavior."[14] If life, pain, injury, malnutrition, disease, and many other distresses and disturbances in human life, however, so must war, evil, death and the range of other human behaviors alluded to come under the aegis of biomedically based medicine -- precisely because and so far as it is believed that these are all genetically determined. And, so far as such behaviors are or seem to be based in genetic error, they quickly become understood as presented medical problems and acute episodes, crises requiring medical response. For medicine in our times has increasingly become a crisis-oriented discipline, evident not only from common portrayals in the popular media, but even more from the educational emphases in our schools of medicine. Its centering focus -- expressed, e.g. by the stress commonly given to acute disease and injury in clinical encounters (and the general muting of preventive and chronic problems but also by the modes and quantity of funding, and by the continuing and considerable pressures for still more potent drugs, regimens, and technologies for the diagnostic and therapeutic armamentarium of medicine -- is acute disease, illness, injury or affliction.

Despite the fact that the bulk of the time most physicians spend with patients is concerned with largely mundane complaints and gripes, and very little with actual acute episodes, medicine's main public and encouraged image is of a discipline (a "science" even) on the critical edge of life and death, warring constantly and valiantly against aggressive, impersonal and intractable enemies. The humdrum, the prosaic, the mundane have little place either in medical education or in the acquired self-understanding of health professionals. The prominence of combative, military or warfare metaphors, and the values they naturally evoke, is clear and striking: bravery, perseverance, valor in the face of at times overwhelming and implaccable odds.

Thus does so much of our condition become quickly medicalized: modeled as disease and thus in need, by definition, of "cures".[15] Disease, injury, malnutrition, and now even death seem plainly accountable by,. become accommodated to, material, biologic nature. But if death, so too does life seem similarly accountable, and the metaphors and images come full circle: life itself is taken as a constant struggle for survival, ultimately against the final enemy, death, and medicine becomes imaged as serving that struggle. Thus, too, do the biomedical sciences whose knowledge and technologies serve that medicine, come to share in the imagery, the sense of urgency and crisis, as well as the evoked values and virtues.

It is in this light unsurprising, but striking all the same, to read another Nobel Laureate, Sir John Eccles, on this topic maintaining that

> Planned genetic manipulation now replaces the natural process of biological mutation by chance...man has taken over control of the biological processes of differentiation, multiplication and survival. Biology is not completely frozen at the end of the evolutionary era. Rather it is now enslaved for man's purposes in that useful species are deliberately changed by genetic engineering in order that they can be more useful for exploitation.[16]

It is important to note, first, that (as Kass pointed out) this usage of clear, patently empty abstractions ("man", "biology", "man's purposes", etc.) effectively obscures the fact that it is individual biologists, individual men and women who exercise this "useful" power over "nature". Not only, of course, are "useful species" so manipulated, secondly; for genetic engineering now promises this "exploitation" and "enslavement" as regards human beings themselves, possibly on the engineers themselves!

To see the workings of such militaristic metaphors, of course, is to witness the fulfillment of Francis Bacon's combative vision: that knowledge and power become one in the struggle to conquer ~~man's~~ humanity's otherwise endemically vulnerable and brutish condition. Medicine in its modern, 20th century form is perhaps the most significant heir to that tradition, uniting remarkable power and knowledge. And, it is obvious, to the extent that its exercise of this power has been and continues to be successful in combatting afflictions, as it surely has been in many ways, it has understandably accrued to itself immense social prestige and prominence. Our age has witnessed the historical "flight of the gods," of univers , and of tradition itself as sources of moral ideals and ethical justification. As these have steadily diminished, that discipline, medicine, seemingly most directly attentive to the elemental condition of human life -- life, death, birth, disease, guilt, failure, etc. -- has come to assume their place. And this has come about almost by a kind of socio-historical accident, for there is very little in the traditional education and training of the medical professionals which specifically equips them to address the great social, political and moral issues inherent to medicine's concern with affliction.

Ethics and Genetic Technology: Reflections on Power

At this point it seems appropriate to focus on the prospects opened up by the genetic technologies which, so far as they lead to enhanced diagnostic, therapeutic or prognostic abilities in medicine, have contributed so much to the social prominence of medicine's power. It is neither my purpose nor my competence to detail specific technologies now at hand or on the horizon. I want rather to underscore two major themes intrinsic to the development of new biomedical knowledge and technology. These were brought out with commendable clarity and directness in the 1978 conference on "New Knowledge in the Biomedical Sciences" held at the University of Missouri/Columbia, and presented in the recent volume of essays selected from it.[17] One of the organizers and editors, H. Tristram Engelhardt, Jr., gives perhaps the clearest expression. First, "new medical knowledge is always potential or actual medical power,"[18] specifically, of course, designed to increase medicine's diagnostic, therapeutic and prognostic abilities. But, secondly, precisely because such knowledge, including the auxilliary knowledge provided by biomedical science, is never simply knowledge but is knowledge yielding multiple technologies which inevitably affect individuals and society; "the very presence of knowledge creates obligations which were unacknowledged in the past when we were more ignorant of the dangers associated with particular diets, particular chemicals, and certain styles of life."[19] As the power increases and spreads, so too must human responsibility and accountability, for as the ability to know (e.g. genetic or congenital defects in utero, through amniocentesis, ultrasound, AFP testing, etc.) increases, not to mention the ability to change (e.g. via abortion, in utero surgery, artificial placentas, gene surgery, etc.), so does the range of choices increase. Thus, "biomedical technology offers a means for making our human nature conform to our chosen goals. It allows our personal choices to triumph over the surd forces of nature."[20]

What should concern us, I believe, is this enhanced power and this increasing range of human choice, responsibility and accountability. More specifically, however, we need to understand very precisely exactly what these technologies and this knowledge have now made possible in principle, the kind of power now at hand (and daily being enhanced), in order to understand not only the multiple social, religious and political issues they necessarily bring with them, but also so as to be able to assess the exact sorts of moral choices, responsibilities and accountabilities which we inherit -- indeed have already inherited, however ill-prepared we may be.

Ethics and Genetic Technology: Reflections on Power

There are three areas of critical concern, two of which have already been mentioned above.. (1) Our technological and biomedical prowess have already made it plausible to conceive, and practice to some extent, the genetic control of future humanity. As Sir John Eccles puts it, we can now take biological evolution into our own hands. Not only are "useful species" deliberately "enslaved" and "changed by genetic engineering" making them "more useful for exploitation;" the same is now plausible, and already in practice in some instances, as regards human beings -- in euphenics, eugenics, as well as in such technologies as have led to in vitro fertilization and embryo transfer.

(2) Beyond this awesome power to "play God" as regards future generations, to a remarkable extent it is plausible, and already practiced, to exercise this control and power as regards present-day individuals and even on entire populations. Through psycho-pharmacological interventions and behavior modification techniques -- including electrical stimulation of the brain to produce pleasurable or painful experiences, brain surgeries, operant-conditioning, aversive conditioning with electric shock, and an increasing array of depressive, antidepressive, hallucinogenic and so-called "mind-expanding" drugs -- it is plausible to circumvent the context of human speech and meaning, to bypass human choice, and go directly to work to modify the human material substrata itself.[21] A prominent psychologist has already seriously suggested the use of such drugs, for instance, to modify the moral sense and outward behaviors of violent persons in order to insure their conformity with social expectations.[22]

(3) A third region has been mentioned: by taking death as a kind of "disease" or result of genetic error in somatic cells (Burnet), biomedical technology seems to offer the most stupendous and awesome prospect: to bring our own mortality within the circuit of our own control -- if not to make ourselves like unto gods by becoming age-immune, at least to extend our longevity by a substantial temporal leap.

Now, this remarkable power implies the possibility, as Bentley Glass once put it, of determining present and future "people to react in predictable ways desired by government or by commercial interests [or by other users of these technologies], without persons quite knowing how they are hoodwinked.."[23] This power, in other words, is the power to alter, perhaps irrevocably, our very capacity to reckon with and to understand the technologies themselves, thereby biomedicine and medicine -- and ultimately our ability to know ourselves. It is a power whose use is defined by its capacity to cancel out all cognizance of its having been used, and thus directly affects us in our most intimate humanity. It is a power which is profoundly paradoxical, creating a most acute dilemma: for the power as well implies, as was already noted, a commensurate expansion of choice and responsibility, yet can plausibly cancel the very foundation on which responsible choice depends.

Hans Jonas' words thus reverberate with clarity and pathos:

> Living now constantly in the shadow of unwanted, built-in, automatic utopianism, we are constantly confronted with issues whose positive choice requires supreme wisdom -- an impossible situation for man in general, because he does not possess that wisdom, and in particular for contemporary man, who denies the very existence of its object: viz., objective value and truth. We need wisdom most when we believe in it least.[24]

Stripped of the unfortunate abstractions in this passage ("man in general," "contemporary man," etc.), Jonas' point is well taken. The argument here is that those persons who not only still believe in the necessity of objective value and truth, but also in the need for and possibility of wisdom, today find themselves in the clear minority. Not only that, for they find the very expression of such notions strongly challenged, most particularly by the very scientific community whose work and consequences for human life are just what have urgently raised the very issues demanding that mode of address. Just this, among other things, constitutes the meaning of our current moral crisis: our current situation is one which most demands the very wisdom which is least believed to be possible.

III

To assess the exact nature of the power-to-change is neither to condemn nor to baptize the new knowledge and technologies. Nor is it to assert that each and every biomedical development should be either prohibited or subjected to rigid regulation -- for not every technology carries either the same kinds of jeopardy or the same potential. To emphasize the full scope and nature of our total technological powers, or even a number of them together (e.g. those leading to enhanced diagnostic ability), is to underscore both the urgency and the scope of responsibility and accountability which we face socially and politically...like it or not. Our knowledge and technical capacity underscores the fact that they themselves have significant public policy as well as moral implications. Indeed, it has been in many ways the growing social prominence of biomedical knowledge -- especially in areas such as in vitro fertilization and embryo transfer, neonatal regimens for providing intensive care for damaged babies, or the recombinant DNA dispute -- which has raised special concerns regarding the role of those who acquire and possess this knowledge, the basis for allocating inevitably expensive and scarce resources for its acquisition, and the criteria for assessing the impact of this knowledge and associated technologies on the larger population. Precisely by its abilities to resolve the otherwise unresolvable infertility of some couples, or its abilities to detect severe neural or genetic damage in utero, much less to keep alive (in some sense) those babies whose conditions only a few years ago would have resulted in death, medicine and its basic biomedical sciences impact the social scene in multiple ways, and thus come under the need for social policies.

To get a better handle on what this socially salient power implies, it seems to me imperative first of all to get what the sociologist, Peter Berger, once called a clear perception of reality. And for this, we have already made one crucial step: the plausible prospects of our current power make altogether evident not only what is needed for the exercise of that power, wisdom, but also that we simply do not possess it -- nor, as Jonas emphasizes, do many people in our times believe in its very possibility. Yet, the very terms of our technologies and genetic discourse plainly presume that at least the speakers and writers of that discourse have that wisdom -- they could not say what they say without presupposing it. When Sir John Eccles, e.g., writes that biological processes are now "enslaved for man's purposes," he presumes to know what those purposes are or ought to be. When he wrote that biological species, including human beings, are or can be "changed" to be made more "useful" for "exploitation," he plainly presumes he and other "users" and "changers" both know what "the human good" is and "human ends or goals" are, and that they all act so as to serve that "good" (and not, to the contrary, what is "evil").

Furthermore, Weissman contends that bioliogical knowledge should be judged by "utilitarian" values -- that is, such knowledge is "useful" knowledge. But this clearly presumes what by no means can be presumed: namely, that we already know for what ends this "useful" knowledge is indeed useful. To conceive knowledge as "useful," that is, presupposes precisely another kind of knowledge which is not and cannot be so conceived: a knowledge of ends, goals, or purposes. And this knowledge is specifically different and outside the purview of any form of "useful" knowledge.

Weissman, unlike Eccles, however, may seem to recognize this point when he responds to the problem of the misuse or abuse of these "useful" powers. For, he says, it has been largely scientists themselves who, "acting in response to a code of moral values they share with others, have 'pulled the whistle' on more of these outrages" -- such as the abuses of the Nazis or that committed under Stalinism.[25] The "utilitarian" values of science have been informed by and based on this "code." But what is the code he is talking about? To this, Weissman responds, as noted earlier, by appealing to the "humane ethics" of the society at large: the moral codes of scientists "are probably determined more by the general culture of which they are a part than by any unique sense of scientific ethics. A society gets not only the government, but the science, it deserves."[26] Hence, his conclusion (cited earlier), that if we want to insure that our scientists do not produce the Golem, chimaeras, or the Andromeda strain, we had better insure that our society doesn't want such fantasies realized.

Several things must be said about this remarkable claim. In the first place, one has to presume that if a "society gets not only the government, but the science, it deserves", Weissman has utterly cut the ground out from every possible critique of either a society or a science. About all that could be said of Nazism, in different terms, is that it is "different from our own society," but in no way could terms such as "evil" or "outrageous" be utilized. That is bad enough a predicament to be in; it is compounded, secondly, by the use of such abstractions as "we" and "society" in his statements. These serve only to obscure the disconcerting fact that it is individual people who may want or not want such fantasies, who may or may not use, abuse, or misuse such powers to realize their fantasies. To repeat Kass' point: "What we really mean by 'Man's power over Nature' is a power exercised by some men over other men, with a knowledge of nature as their instrument."[28] To appeal for moral legitimacy to such abstractions is effectively to obscure the reality of power's use and abuse, and in a way to give licence to anybody to define these terms as suits them. This seems even more likely in a pluralistic society: the very moral heterogeneity we otherwise seem to prize, be it noted, makes it inordinately difficult at best to criticize, much less to prohibit by public policy, any number of activities and their respective ends. It is by the very abstractness, for instance, with which the concept of "prurient" or "lewdness" are defined in social policy and legislative enactments which give seeming credibility and license to the "Deep Throats" of pornographic notoriety; surely the very same abstractness will be at work to undermine the very idea of "abuse" of genetic power.

Not only do such abstractions lend themselves to legitimacy appeals; their remoteness of meaning does not seem to stem their evocative power: "true believers" on rival sides of an issue equally appeal to and derive from them the kind of spiritual sustanence and passion which all too easily can be channeled into corridors of violence -- physical or merely verbal -- in contexts of dissent and dispute. This is surely as much a part of the current abortion debate as it was in the early stages of the controversy over recombinant DNA technology. The exaggerations of rhetoric, the passionate adherence to abstractly framed values, the impatience with complexity and the desire for simple, quick answers: none of these serve the cause of responsible, accountable decisions, nor to legitimate uses of the biomedical technologies already at hand or on the horizon.

Weissman's appeal to a moral code "we" share and whose key concepts and force are supposedly defined by "society at large", then, is an appeal quite as fanciful as the so-called popular myths he accuses his detractors of employing (chimaeras, etc.). Beyond that, there is a third and perhaps even more problematic feature of this idea that scientists can do no more than embody the "character and manners," the customs and beliefs,of the larger society. In the first place, that notion plainly confuses the etymological history of "ethics" (Greek: ethikos; Latin: moralis) to which he refers, with the very different questions of ethical obligation, responsibility, and accountability, justifiability , and the like -- issues which have been recognized as distinct since early in Greek culture. In the second place, this appeal to prevailing cultural customs to legitimate or condemn scientific practices makes Weissman's "code" indistinguishable from views he is otherwise obviously opposed to: the "wonderful folks" who gave us the atomic bomb, the laboratory of Auschwitz, and the psychiatry of the Gulag archipelago.[29] Both make the very same appeal Weissman makes -- all of them, moreover, reduce ethics and morality to a mere matter of power: those in social control define the "social consensus," hence the only thing Weissman seems to mean by "ethics".

I am not, I should emphasize, morally condemning persons who seem to hold that view, nor am I denying the significant part many scientists and physicians critiquing abuses of technological power. I am maintaining the rather obvious point that those critiques of abuse owe their force and whatever justification they have to something quite other than "the social consensus." Nor, finally, can I be understood as in any sense "anti-science" -- I am after all on record as a staunch defender of such exotic technologies as clinical in vitro fertilization and embryo transfer.[30]

I am suggesting that grappling with the moral issues -- at the level of public policy or as regards individual values -- is in no way well served by those abstractions or the appeal to social consensus. To make my point as cogently and concisely as I can, I am deeply committed to the idea that the kind of awesome power represented by current and prospective biomedical and medical technology positively requires, as a first and essential step, that those principally engaged in these researches and applications must recognize themselves as morally bound to a common code which speaks specifically to the crucial meaning of "abuse", of "man's purposes," and the like, and which is neither exclusively personal nor only a matter of general social consensus. I thus have been immensely impressed by the far-reaching significance of the well-known Asilomar Conference, for here it was realized both that the community of scientists themselves needed to reach a shared understanding and agreement about their own work and its consequences for the broader society, and that hither to there simply were no professionally and socially recognized and legitimated social forums within which issues of that type could be discussed, and binding agreements reached. At the same time that I am impressed, however, I have also been dismayed: there still are no such forums, there still is no such common code, and even more the mere mention of such a code seems invariably to conjure up the ugly spectre of censorship to many scientists.

Thus, Weissman expressly states that "we are discussing censorship when we liken the profession of science to the profession of law or of medicine."[31] He thus staunchly opposes June Goodfield's recommendation that the scientific profession be governed by a kind of professional code like that of the law and medical professions.[32] He opposes this because he believes that this in fact amounts to "the imposition, by means of external authority, of a professional code upon the scientist."[33] This presumes what he apparently believes is false, namely, "that the utilitarian output of the scientist's profession has some 'unique' social implications, and that these implications require society at large to set some limit on his esthetically motivated quest."[34]

This argument is quite peculiar, and its peculiarity is significant. Believing that the "output" of science has been "intrinsically benign," the scientist seems relieved of questions about ends and goals, and can then proceed to concentrate merely on what the "toyshops of technology, and the purses of government" allow him to do with the "means at his daily disposal." In this way, Weissman says, "the game of science has been played in obedience to a set of rules which have remained uncluttered by any ethical structure save one: thou shalt not fudge the data!"[35] And of course, as he later says, the social consensus which is embodied in scientists no less than in others in the same society. Thus, he urges us to accept the view that "the possible misuses, in the utilitarian sense, of his knowledge should not lead to preemptive rules as to the kind of inquiry the professional may engage in."[36]

In this, Weissman makes two critical mistakes. First, to evoke the spectre of censorship, the ugly ghost of externally imposed regulations and codes, is a plain *non sequitor*, and appeals to fear, not reasons, to boot. My point (and Goodfield's, so I gather) is not at all that science requires externally imposed codes and strictures. It is rather that the profession itself, and especially that part of it whose research and technology is strictly in support of medicine (and thus impacts persons, both individuals and populations) -- i.e. biomedical science -- is inherently obligated to recognize formally and therefore professionally its own intrinsic nature and purposes. It is morally obligated to recognize that its knowledge as well as its technologies inherently have a fundamental moral dimension -- signaled most perhaps by the actual and potential affects, i.e. the social power, they have on human life and persons, as well as on the rest of biological nature.

I am not so naive as to believe that a mere "code" of ethics of itself will solve anything. The point rather concerns the fact that these sciences themselves at once have a crucial moral dimension and at the same time deeply affect prevailing moral life (precisely by affecting human life and persons). That is, biomedical science, no less than medicine, constitutes a moral profession, its knowledge no less than its technologies serve the ends of enhancing human life and ameliorating the effects of disease and other forms of distress and damage which compromise human beings. The fact is, too, that in a pluralistic society the functions of such a code may well be one of the few means at hand to make the moral character and moral consequences of biomedical science socially known, respected, and understood.

In this respect, what is different about biomedical science is that it, unlike the professions of law and especially of medicine, has no historic tradition of public moral commitment (as is, e.g., exemplified by the Hippocratic oath), and thus the idea of such a moral purpose for the profession itself has never been understood as in the least necessary. The historical fact that the sciences have so long been taken to be "value-free," especially by scientists themselves, has only obscured the point. That day in any case is long gone; indeed, Stephen Toulmin has shown, with others, that for many accountable reasons "the professional organization and priorities of scientific work can no longer be concerned solely with considerations of intellectual content and merit, as contrasted with the ethical acceptability and social value, either of the research process itself, or of its practical consequences."[37] What is thus called for, I believe, is a most careful inquiry into the ways in which ethical issues enter into the conduct of scientific research, as well as the ways in which science itself has impacted moral and social life. Moreover, this requirement must as well, as Toulmin says, involve us in a careful reconsideration of "just what the proper scope and limits of professional autonomy are, and at what points scientists cross the line separating legitimate professional issues from matters of proper public concern, whether political or ethical."[38]

In short, a moral code for biomedical scientists seems to me long overdue, precisely in view of the recognized fact that both its technologies and its very knowledge create new obligations, affect moral life, and embody awesome power to alter human life now and in the future.

A second critical mistake in Weissman's claim is his denial that the biomedical scientist's "output" has some unique social implications. His denial is curious. On the one hand, he maintains that the social consequences of his science are no different in kind from those of the creative artists, historians, philosophers, and social scientists. If this were true, if it were the case "that the contributions of Fichte, Nietzsche, and Spengler"[39] were no different in kind from those of Edwards and Steptoe, Salk and others in genetics, microbiology, and so on, then the obvious conclusion is that all such persons would be, or ought to recognize themselves collectively as, bound by a common moral code! But it is surely odd to claim that sort of thing; perhaps there is an unintended witticism here: from my own experience in philosophy, perhaps the rudest shock a philosopher could have is to find himself being taken seriously and "put to use" by anyone! More to the point: the issue concerns the inherent kind of knowledge biomedicine has and makes available to others, i.e. the deep and ineluctable tie between scientific knowledge and technology, a tie in no way found in the arts or the humanities --or, if it were found, as was pointed out, it is one which would obligate those persons personally and professionally no less than it does physicians.

The other point is plain enough in any case: whatever may or may not be said about the arts, philosophy, history, etc., the plain fact is that the biomedical sciences, and other sciences as well, do indeed have unique social implications -- precisely that is the commonplace point with which this essay, like so many others, began. As Hans Jonas has emphasized so many times, "the boundaries between theory and practice [in science] have become blurred...The two are now fused in the very heart of science itself, so that the ancient alibi of pure theory [Weissman's "esthetic values"], and with it the moral immunity it provided, no longer hold."[40]

In response to my second general area of concern, then, it seems to me unambiguously clear that the biomedical community of scientists does indeed constitute a profession (Toulmin, Goodfield), that the conduct of their research as well as the consequences of that research (knowledge and technologies) are deeply tied in with moral life (that of the community itself, and of the larger society beyond) and have ethical dimensions, and that therefore this community of scientists bears the responsibilities and accountabilities in the first place which can and should receive the kind of formal, public recognition as is exemplified in professional codes of ethics. It is not my argument that such strictures should be imposed from outside on that community. But, failing to do it itself may well bring in its wake a more sweeping, immoderate, and throttling sort of control from the non-scientific public.[41]

The fact is, of course, that much control and regulation -- direct and indirect -- is already practiced: through institutional and federal agencies, for instance, as also through funding agencies. In Kass' correct terms: "Clearly, the question is not control versus no control, but rather what kind of control, when, by whom, and for what purpose."[42] My point has been that those persons who best know what goes on within science, who most closely identify with its values and aims, and who are most able to appreciate the direct technological consequences of their knowledge -- i.e. the scientists themselves -- bear the obligation to police themselves first and foremost. That other social agencies also have legitimate responsibilities here is granted; it is, however, that community which has most resisted this formal responsibility that is most immediately accountable by all of us. The Conference at Asilomar could thus well be a seminal development, when properly appreciated as a forum specifically designed to acknowledge the points being made here.

IV

A final area of concern can be treated less extensively, for much of it has already been brought out to some extent. We desperately need a well-based and thoroughly justified framework within which to provide the much needed moral discernment, discussion, and assessment of such things as genetic technology.

I take it as perfectly obvious that no one of us singly, myself included, has the requisite wits and wisdom to provide that framework single-handedly. The requirements of a pluralistic society seem in any case to legislate against such heroic efforts. The dimensions of our current moral malaise and even crisis especially as laid out in MacIntyre's fine book, After Virture,[43] give all the more reason to believe that the needed wisdom is far from all of us. Yet, the urgency of the issues, and the very dynamism of what raises them in the first place, i.e. biomedical knowledge and technology, have willy-nilly forced each of us who can to make that effort, to contribute what each can. For just as not regulating genetic technology is as much a policy decision as the opposite, so too would not grappling with the problem of providing a moral foundation for discernment and assessment be as much a moral decisions (and a dubious one at that) as the opposite.

A good deal of labor in bioethics has already been done on this, and is readily available; a good many hard and important insights have been won by those whose writings I have cited here. I offer the following merely as a hopeful contribution to such efforts.

We face a genuinely common issue, one which positively demands collective dialogue having common aims and needing public support. Not only in view of the immense complexity of the issues, nor only because of the nature of a pluralistic society, but also in view of the unique kinds and significance of the issues, a shared dialogue is absolutely demanded, I believe. In this, Stephen Toulmin's recent article, "How Medicine Saved the Life of Medicine," is wonderfully correct. He points out how the very urgency and seriousness of the moral issues inherent to human affliction, and medical treatments of them, require renewed ethical attention, possibly even renewed kinds of methods. But, his article also harbors a perhaps unsuspected message: "We are who we are: we stand in the human relationships we do, and our specific moral duties and obligations can be discussed in practice only at the point at which these questions of personal standing and relationship have been recognized and taken into account."[44]

To clarify and hopefully to reach resolutions to these issues, we are called upon to be uniquely open to the words and thoughts of others, in whatever walk of life or professional discipline it may be. We positively need to learn and to share reflections in common. This communal forum has long been a key part of science, although its focus has only rarely been on the moral dimensions of that community itself, or the broader society. Since such a community, like many others, is indeed not only an intellectual but also a moral one, with multiple shared values and purposes, no less binding than "not fudging the data", it would not seem unreasonable to expect that deliberate dialogue about ourselves as moral beings, as well as about our community together, present and future, would be both requisite and fruitful.[45]

To reach the kind of moral foundation our current situation cal~~ls for~~, in a word, we stand in clear need of renewing ourselves as a moral community. For the viewpoint I am suggesting, the tradition of modern individualism with its stress on individual rights and a libertarian view of society, too often tended to ignore precisely what is on the other hand descriptively evident, namely, that each individual essentially lives within multiple constitutive groups (such as voluntary associations), institutions (such as family, law, etc.), and communities (such as academic, professional, religious, etc.), each of which have their own distinctive moral networks of obligations, rights, responsibilities, values, goods, etc., and within which alone are an individual's own values developed and nurtured. My initial confession of modesty, then is not simply that: the acknowledgement of the need for shared dialogue is rather a recognition of the demands inherent to a moral community (even, or especially where it is in relative disorder). As the clinical, or any other, encounter with an afflicted human being poignantly demonstrates, we are ineluctably bound together in complex contextures of mutual interrelationships and actions, and morality is precisely the binding texture of that cultural cloth. As Toulmin rightly says, echoing the point made on many occasions by Alfred Schutz,[47] "we find ourselves born into communities in which the available ways of acting are largely laid out in advance: in which human activitiy takes on different Lebensformen, or 'forms of life' (of which the professions are one special case), and our obligations are shaped by the requirements of those forms."[48] Or, as Schutz would have said, our lives are shaped by the requirements of the different contexts of relevancy prevailing within each of these multiple social realities.

A first requirement for a context within which to discern, discuss, and assess the moral issues presented by genetic engineering, then, is that of continuing, multi-disciplinary, and multi-professional, dialogue -- and not only among academics or scientists. For the issues in question far exceed the parameters of such provinces of discourse, and require the involvement of other provinces as well.

No discussion of moral issues, or better, of the moral dimension of genetic issues, however, can at all hope to discern that dimension in abstraction from the actual work, technologies, and prospects of genetic technology. More generally expressed, moral issues are what they are (whatever they may turn out to be in specific cases) solely within the contexts of their actual occurrence. It is therefore imperative, if we would hope to grapple seriously and fruitfully with them, that ethicists, policy-makers, legislators, and others not only be informed about the actualities of genetic engineering and its social and moral consequences, but also to gain as much direct experience with the actual contexts of these labors as possible. To do this is to inquire, in considerably greater detail than has been customary for most of such persons, moral philosophers included, into the situations within which ethical dilemmas, problems, or enigmas actually arise, and to pay far closer attention to the human interchanges embodied in them.

To give but one brief example of only one facet of a most complex issue, if one truly would "assess the risks" of in vitro fertilization and embryo transfer, it is ungetaroundable (to borrow C.I. Lewis' wonderful term) that one must come to understand not merely what sorts of actual procedures are performed with the ovaries, the sperm and the eggs, the embryo, etc., nor merely the admittedly serious issue of informed consent from the would-be parents. It is wholly necessary to appreciate just what the infertility of these parents actually is for them -- their hopes, guilts, fears, apprehensions, values, in short how it has shaped their lives, ultimately their own sense of themselves as "family" and "parents." "Risks" cannot be understood or assessed abstractly any more than can the meaning of "family" or "parenting" in this or that specific case; all have their placement with the concrete, particular reality of these people and their specific lives.

A second requirement for a sound moral context, then, is that of continual immersion within the specific and the particular, including not only the specifics of each type of actual or proposed genetic technology, but also the specific persons or types of persons who will be directly or indirectly affected or for whom the technologies are proposed, the specific problems pertaining to each, as well as the specific aims to be realized in each case. What is found to be the case with one technology (IVF, for instance) may or may not be the case for another (genetic screening, for instance). Despite the initially obvious point that different technologies have multiple similarities and ties (IVF and artificial placentas, for instance), it seems to me imperative to discern, discuss, and assess each in its own terms and contexts of application, consequences, and the like. Only in that way is it really possible to understand the problems, possible therapeutic or diagnostic uses, and the rationale each is proposed to meet, whether and to what extent that is actually going to be accomplished, and whether alternatives are at hand and perhaps preferable.

The very immensity of the task is surely of itself enough to make a third requirement evident. We as a people, or at least many of us, may well not be adequate to the task; as many scholars and researchers have pointed out, we may not possess the requisite wisdom to enter the age biomedicine and medicine have already opened up for us: of literal remaking ourselves and our progeny. Even so, the bald fact is that we are already in the midst of that demanding age, and innocence or ignorance in the face of it seems hardly an excuse. Our relative lack of wisdom may be an unhappy fact; it is also, I think, an urgent challenge. Expressed more concretely, our apparent situation seems unavoidably to dictate, as Kass has already said, echoing Hans Jonas, that "we sorely need to recover some humility in the face of our awesome power," and in light of that to recognize and avoid at all costs "the folly of arrogance."[49] But the conclusion Kass drew from this seems to me wrong in a key way: "When we lack sufficient wisdom to do, wisdom consists in not doing. Caution, restraint, delay, abstention are what this second-best (and, perhaps, only) wisdom dictates with respect to the technology for human engineering."[50] For what Kass seems clearly to mean by those remarks is truly "not doing," i.e. "abstention." Even though he clearly and correctly pointed out that he is not at all "antiscientific," but only against the use of some technologies, it is just as clear that he stood opposed to "human engineering" in any form, and quite explicitly to IVF.[51] And here I must part with otherwise congenial company.

I agree with him, that biomedical technology is hardly an unmixed blessing. I agree, too, that humility and strong resistance to the folly of arrogance are demanded by our lack of wisdom. I agree, finally, that caution is a clear requisite -- at every stage of each actual and proposed technology. But neither our relative lack of wisdom (for surely not all of us are equally unwise, any more than all of us are equally avaricious -- Kass here tends to fall victim to his own strictures against abstraction!), nor the need for caution implies abstention, and probably not even delay. To urge restraint seems inarguable; but to urge abstention seems little more than another kind of folly.

One of the more intriguing moral ideals found in the works of Plato, and which might help us at this very point, is that of sophrosyne[52] -- it is also, however, one of the most puzzling and apparently resistent to clear translation. Variously rendered as "temperance," "restraint," and "balance," it seems to have been intended to name at least one key characteristic of "wisdom" (sophia). Its meaning seems in any case closely connected with both "justice" and "courage," and judging from various contexts may well have been used to express the moral stance required in the face of a lack of wisdom and impending dangers: moderation, self-control, calmness, restraint, caution, prudence, wariness -- alertness, that is, to possible danger, attentiveness to perils, but calmness balanced by courage and refusal to be taken in by deception or by the agitations of uninformed passion and emotion.

It is just this complex attitude or virtue, I think, which our present situation clearly demands. Negatively, it bespeaks resistance to hasty and premature judgment, to allowing oneself to be taken over and unbalanced by fear. Positively, it involves a readiness to act even in contexts of uncertainty and possible harms, a willingness to learn even where ambiguities beset us, an alertness to risks and perils and a continuously present ability and readiness to say either "no" (to cease, stop, at any point) or "yes" (to proceed, to recommence, etc.).

Biomedical technologies aplenty are already with us; more are promised almost daily. Moreover, matters of immense intrinsic interest, as well as of fruitful consequence, are being acquired -- about our bodily and social conditions, about our environs, and natural heritage, about ourselves. That there are equally significant issues which need our attention, issues which may be obfuscated by the glamour of these technologies, and which do not need novel technical solutions -- such as general health care, preventive measures for individuals and populations, etc. -- is doubtless true.[53] These may well be of even greater significance at the moment, and far more cost-efficient, than some of the current biomedical exotica. Nonetheless, even if that turned out to be ture -- and it may well be -- the argument it provides against genetic technologies by no means leads to Kass' conclusion of abstention. Indeed, certain of these technologies may well be centrally instrumental in helping to resolve just such issues, or some of them. In any case, such an argument only goes to reinforce the need for restraint, constant reassessment, caution, and avoidance of extremist views of every sort.

Respect for the need for self-imposed professional codes; recognition of the constraints and demands as well as prospects of moral community and the essential place of shared dialogue undertaken seriously and maturely; immersion within the specific contexts of biomedical and medical research with an alert eye for its intrinsic rationale and impact on human and animate life; and careful cultivation of the attitude or virtue of sophronsyne: these are essential ingredients of any morally foundational context from within which the moral issues posed by these technologies can best be addressed (and redressed, where need be). Although he has not, regretably, been widely read and appreciated, the philosopher and dramatist, Gabriel Marcel, best expressed this requisite orientation with his central concept: *disponibilité*. Translated, Marcel meant by this a kind of creative openness and availability towards such technologies (and everything else) in the sense of a stance toward them which at once is neither merely gullible nor unthinkingly resistant, which rather keeps an open and critically alert mind on them, enabling their development as wisely as communally possible and being ready at any time to cease or delay whenever wisdom, so far as we collectively possess and articulate it, requires. As awesome as is our power to alter ourselves, so must our understanding of it be fair and open: to the fact, e.g., that equally awesome medical responses to otherwise hopeless forms of affliction and distress have been made just as much a daily reality. But the requirement of such power is also the demand on us to assume the equally awesome responsiblity of gaining wisdom and maturity -- individually and as a culture. Without that maturity, I fear, Weissman's otherwise innocuous phrase -- the "toyshops of our technology" -- may return to haunt us all, and we will find ourselves the playthings of our own "Pac-manesque" toys.

FOOTNOTES

1. Mark S. Frankel, *Genetic Technology: Promises and Problems*. Washington, D.C.: Program of Policy Studies in Science and Technology, The George Washington University, Monograph 15, 1973.

2. See Hans Jonas, *The Phenomenon of Life. Toward a Philosophical Biology*. New York: Harper & Row Pubs., Inc., 1966.

3. See Leon Kass, "The New Biology: What Price Relieving Man's Estate?", *Science,* 174 (November, 1971), pp. 779-88.

4. For instance, Paul Ramsey, *Fabricated Man: The Ethics of Genetic Control*. New Haven: Yale University Press, 1970. James Gustafson, "Genetic Engineering and the Normative View of the Human," *Ethical Issues in Biology and Medicine* (Preston N. Williams, Ed.). New York: Schenkman, 1973, pp. 46-58. Daniel Callahan, *The Tyranny of Survival* New York: MacMillan Publ. Co. 1973.

5. Gerald Weissman, "The Need to Know: Utilitarian and Esthetic Values of Biomedical Science," in: William B. Bondeson, H. Tristram Engelhardt, Jr., Stuart Spicker, and Joseph M. White (eds.), *New Knowledge in the Biomedical Sciences*. Dordrecht/ Holland, Boston/USA, London/England: D. Reidel Pub. Co., 1982, pp. 105-12.

6. Ibid., pp. 107-08.

7. June Goodfield, *Playing God*. New York: Random House, 1977, pp. 169-70.

8. op. cit, p. 110.

9. Ibid., p. 111.

10. Ibid., p. 107.

11. Leon Kass, op. cit.. p. 782.

12. Ibid., p. 783.

13. Macfarlane Burnet, *Endurance of Life: The Implications of Genetics for Human Life*. London: Cambridge University Press, 1978, p. 2.

14. Ibid., pp. 75, 88.

15. Ivan Ilych, *Medical Nemesis: The Expropriation of Health*. New York: Bantam Books, 1976.

16. John Eccles, *The Human Mystery*. The Gifford Lectures, 1978. New York/Berlin/Heidelberg: Springer-Verlag, 1979, p. 120.

17. See above, footnote 5.

18. Ibid., p. xvii.

19. Ibid., p. 179.

20. Ibid., p. 180

21. Cf. Kass, op cit., p. 779.

22. See, for instance, Kenneth B. Clark, "Psychotechnology and the Pathos of Power," in Floyd W. Matson (ed.), *Without/Within: Behaviorism and Humanism*. Monterey, CA: Brooks/Cole Pub. Co., 1973, pp. 92-98.

23. Bentley Glass, "Human Heredity and Ethical Problems," First Annual Oration of the Society for Health and Human Values, 1970, published in *Perspectives in Biology and Medicine* 15, 2 (Winter, 1972).

24. Hans Jonas, *Philosophical Essays. From Ancient Creed to Technological Man*. Englewood Cliffs, N.J.: Prentice-Hall, Inc., 1974, p. 18.

25. Weissman, op. cit., p. 110.

26. Ibid., p. 110-11.

27. Ibid., p. 111.

28. Kass, op. cit., p. 782.

29. Weissman, op. cit., p. 110.

30. Richard M. Zaner, "Clinical In Vitro Fertilization and Moral Conservatism: A Critique," submitted for publication, and as part of my testimony before this Sub-committee.

31. Weissmann, op. cit., p. 109.

32. Goodfield, op. cit., pp. 78, 89.

33. Weissmann, op. cit., p. 108.

34. Ibid., p. 109.

35. Ibid., p. 106.

36. Ibid., p. 110.

37. Stephen Toulmin, "Can Science and Ethics be Reconnected?" *The Hastings Center Report* 9, 3 (June, 1979), p. 32.

38. Ibid., p. 32.

39. Weissmann, op. cit., p. 109.

40. Hans Jonas, "Freedom of Scientific Inquiry: The Accountability of Science." *The Hastings Center Report* 6 (August, 1976), pp. 15-17.

41. Kass, op. cit., p. 787-

42. Ibid.

43. Alasdair MacIntyre, *After Virtue*. Notre Dame, ID: Notre Dame University Press, 1981.

44. Stephen Toulmin, "How Medicine Saved the Life of Ethics," *Perspectives in Biology and Medicine* 25, 4 (Summer, 1982), pp. 736-50.

45. James Gustafson, op. cit., p. 54.

46. Cf. Herbert Spiegelberg, "Good Fortune Obligates: Albert Schweitzer's Second Ethical Principle," *Ethics* 85 (1975), pp. 227-34.

47. Alfred Schutz and Thomas Luckmann, *The Structures of the Life World*, tr. R.M. Zaner and H.T. Engelhardt, Jr., Evanston: Northwestern University Press, 1973.

48. Toulmin, "How Medicine Saved...", op. cit., pp. 745-46.

49. Kass, op. cit., p. 786.

50. Ibid.

51. Leon Kass, "Babies By Means of In Vitro Fertilization: Unethical Experimentation on the Unborn?" *New England Journal of Medicine* 285 (1971), pp. 1174-79; and his "The New Biology and 'Old' Morality," Public Interest 26 (1972), pp. 32-33.

52. In the wonderful dialogue, *The Charmides*.

53. See Marc Lappe, "Moral Obligations and the Fallacies of 'Genetic Control'," *Theological Studies* 33, 3 (September 1972), pp. 411-27.

Mr. GORE. Thank you very much. We will hold questions.

The final member of this panel and the final witness of today's hearing is Dr. Jonathan Beckwith, professor of microbiology and molecular genetics at Harvard Medical University Medical School, Boston.

Please proceed.

Dr. BECKWITH. Thank you, Mr. Chairman, and thank you for the invitation to appear before this committee.

I am a researcher in genetics at Harvard Medical School. I study the functioning of genes in bacteria and often use the techniques of genetic engineering in this work.

I believe that genetics is one of the most important contemporary scientific fields and has contributed and will continue to contribute to an improvement in the quality of life and to our basic understanding of who we are and where we came from.

On the other hand, I am also aware that throughout the history of this field genetics has been used to oppress people and worse. It is this double-edged sword which must be confronted by both the scientist and the citizen in their consideration of contemporary progress in this field.

To understand the implications of current advances in genetics, it is essential to take a look at the history of the field.

The flowering of genetics began at the turn of the 20th century with the rediscovery of Mendel's laws of inheritance. The growth of genetics led rapidly to benefits for humanity. Plant and animal breeding and the detection and understanding of genetic disease are among the examples of the fruits of this new scientific field.

However, at the same time the ideas of genetics were extended to a number of human problems with disastrous consequences. Many leading geneticists at the turn of the century became part of the eugenics movement. Followers of eugenics believed that people were born with either superior or inferior genes.

They believed that many of our social problems could be explained by the existence of people within the population with defective genes. They saw a whole range of problems as being due to simple genetic traits. These included poverty, criminality and even seafaringness.

These ideas took strong hold in this country during that period, and as a result of the lobbying of eugenicists, a number of laws were passed which caused great harm. These included miscegenation laws passed in over 30 States which prevented the marriage of whites and blacks and, in a number of States, whites and orientals.

Sterilization laws allowed the sterilization of people with low IQs, of criminals and, depending on the State, other personality traits. These laws were still being implemented in certain States up until the 1970's.

In 1924 the U.S. Congress passed the Immigration Restriction Act, which greatly reduced the influx of immigrants from southern and eastern Europe. Eugenicists testified before Congress that the continued influx of immigrants was causing a deterioration in the genetic stock in this country.

Another example of the harmful effects of eugenics ideology was the case of pellagra. Pellagra was a disease found commonly among poor people in the South. Eugenicists, who tended to see everything in genetic terms, were convinced that pellagra was a genetic disease because it ran in families. In fact, pellagra is a nutritional disease due to the absence of a vitamin in the diet.

That it was nutritional was discovered by Dr. Joseph Goldberger in 1915. However, so strong was the influence of the eugenicists that they managed to convince government policymakers of their view that pellagra was genetic and thus prevented appropriate treatment of the disease for 20 years. During this period, tens of thousands of people suffered needlessly or died as a result of the influence of the eugenicists.

The most extreme example of the use of genetic ideas to harm and oppress people was in Nazi Germany. The extermination of millions of Jews, Slavs, homosexuals and mentally retarded was based in good part on arguments that these people were genetically inferior.

However, it is important to realize for understanding the implications of our contemporary situation, that it was not the Nazis who first dreamed up these programs. The racial hygiene movement had existed in Germany for many decades before the Nazis came to power.

As the eugenics movement in this country had many geneticists in it, the racial hygiene movement was dominated by scientists and doctors. Psychiatrists and others spoke of the destruction of lives devoid of value in the twenties. These arguments were always couched in medical terms.

The example of Nazi Germany led to a revulsion after World War II at the consequences of the genetic theories of human problems and, for at least two decades, arguments of this sort were not received with favor.

However, beginning in the sixties, arguments reminiscent of the earlier period began to surface again. In the late sixties and early seventies, Arthur Jensen and others claimed new evidence that blacks were genetically inferior in intelligence to whites.

Jensen's articles were read into the Congressional Record and were used as support of the arguments for ending compensatory education programs. The certain influence on racial attitudes, in general, on teachers and on the self-esteem of blacks cannot be measured.

At the same time, the claims for an understanding of a genetic basis for criminality resurfaced with the discovery of the XYY male. Here it was stated that males born with an extra Y chromosome were doomed to lives of criminality.

As a result, genetic screening programs were initiated to detect baby boys with the XYY character with untold harmful effects on the family attitudes. Now, today, when an XYY fetus is detected by amniocentesis, parents often choose to abort the fetus on the basis of their understanding of the XYY character.

But in both these cases it is now clear that the scientific basis for the claims of some understanding of the genetics of intelligence or criminality were groundless. Even Arthur Jensen no longer stands by his original article. In the case of XYY males, the overwhelming majority of such men are living normal, socially productive lives.

In general, these attempts to pin a genetic tag on a social problem are doomed to failure, in my opinion. The difficulties in separating out the genetic contribution to such qualities as intelligence from cultural and environmental factors appear insuperable at the moment.

These arguments have been appearing in an era of explosive progress in the field of genetics over the last 25 years. The new genetic technologies again provide enormous benefits to this society.

Screening techniques for human genetic diseases have made great advances and there may be much potential in recombinant DNA technology for developing new vaccines and other beneficial products. At the same time, the ghost of eugenics is still with us.

The idea of a genetic fix to solve society's problems is seen in numerous ways. I believe this committee recently heard of genetic screening programs in industry which, while based on little hard scientific evidence, have the potential for discrimination against certain groups and a deflection of attention from the problems of industrial pollutants.

In considering the prospects for gene therapy and any dangers that might come with it, it is difficult to separate this issue from the implications of genetic screening programs. In fact, in all of the problems I have discussed there are three components that can be distinguished.

First, there is an ideology which tends to see the roots of all social problems in the genetic differences between people or even in basic genetic aspects of human nature. Such an ideology then leads to a genetic screening program in one form or another, and finally to some form of treatment or some form of dealing with the problem based on the screening.

In table I I have tried to indicate these components in the various problems I have discussed. What can be seen from this approach is that for some of the contemporary issues, for example, aggression or susceptibility to industrial pollutants, when the technology becomes available, the new, more sophisticated intervention of gene therapy may well be used.

I go on to cite some examples in my text, and then I emphasize that these are only meant to be illustrative examples, not predictions. If the past is any guide, the dangers may well come from areas we cannot foresee at this point.

My fear is that much of this may come about through what appears to be progress in medical research and medical treatment. In the same way that German doctors proposed sterilization and euthanasia for medical reasons and that doctors' communication with prospective parents has led to the abortion of XYY fetuses, eugenics practices with dangerous consequences may well grow without our even being aware of it.

To give you an example of the attitudes which exist among certain doctors and members of the scientific community, I quote to you from some comments made at a meeting held in Cold Spring Harbor earlier this year entitled "Prospects for Gene Therapy: Fact and Fiction."

This exchange refers to a discussion of children born with the genetic disease phenylketonuria, which is eminently treatable with the appropriate diet. The first speaker is Dr. Davis, who will be speaking here tomorrow, and I hope this does not misrepresent his remarks.

> If one systematically did IQ tests on these kids as they became adults, compared them with their parents, it would make a great deal of difference, I think, whether they averaged 5 points less than their parents or 20 or 25 points less than their parents. I would think that kind of information would be worth trying to get, so parents could make their decisions as to whether they wanted to have that kind of child.

Then Dr. Cederbaum:

> We should recognize that this is a form of problem and imperfection that parents should have a right to terminate, if such were technically available.

Why did not these scientists suggest systematically following up these kids to determine whether they became happy adults or whether they contributed to the welfare of their society? Why was IQ used as a criteria? Why did they not suggest a study to improve the diet if the IQ was really lower?

I am not suggesting that in this way values are imposed by the scientific community on people. It is much more subtle than that. I think what happens is that the values of a particular sector, because of their power in the society, influences the decisions of others.

Finally, a few comments about the development of new genetic screening techniques. As a result of the new DNA technologies, it is possible to analyze all of the chromosomes of a human being down to a very fine level. This means that our powers to distinguish between people on the basis of their genetics will increase enormously.

A project being carried out by a number of scientists in collaboration with the Mormon Church, which you may have heard about yesterday from Dr. Skolnick, will lead to improved ways of detecting genetic diseases. But, at the same time, the ability to distinguish individual or groups of individuals at such a fine level will inevitably attract those with the eugenics attitudes I have described. The possibilities for discrimination or for eugenics programs will again raise their heads.

While we cannot help but be excited and hopeful about the prospects that gene therapy opens up for reducing human suffering, we cannot ignore the potential dangers which come along with it.

In the past, those who have suffered at the hands of genetics have been those with the least power in this society. I have no qualms about describing Tay-Sachs or cystic fibrosis as medical problems which require a medical approach. I do have very serious questions about allowing doctors to make decisions that a lower IQ is a medical problem. There must be a clear-cut demarcation made between medical problems and issues which involve societal judgments.

I would like to add a few comments in terms of suggestions for continuing discussion of these issues.

First of all, I would support what previous speakers have suggested in terms of continuing the mechanisms for national discussion of these issues.

Two days ago I was involved with a group of people in Boston involving geneticists who strongly supported the idea of continuing hearings by this committee into the specific subject covered here and broader subjects of genetic screening.

I would also like to suggest another mechanism because in addition to the national mechanism I think there has to be ways for people within communities to discuss these issues. It seems to me that one of the ways of doing this is to use the institutional review boards for human studies with some change in their constitution to foster more discussion of these issues.

I would like to see more input into these committees of people from the community. I realize that is currently mandated in the guidelines, but there could be more input, in ways to insure these committees interact with the community in discussing these issues when they come up.

Thank you.

[The prepared statement of Dr. Beckwith follows:]

STATEMENT OF JONATHAN BECKWITH

I am a researcher in genetics at Harvard Medical School. I study the functioning of genes in bacteria and often use the techniques of genetic engineering in this work. I believe that genetics is one of the most important comtemporary scientific fields and has contributed and will continue to contribute to an improvement in the quality of life and to our basic understanding of who we are and where we came from. On the other hand, I am also aware that throughout the history of this field, genetics has been used to oppress people and worse. It is this double-edged sword which must be confronted by both the scientist and the citizen in their consideration of contemporary progress in this field.

To understand the implications of current advances in genetics, it is essential to take a look at the history of the field. The flowering of genetics began at the turn of the 20th century with the rediscovery of Mendel's laws of inheritance. The growth of genetics led rapidly to benefits for humanity. Plant and animal breeding and the detection and understanding of genetic diseases are among the examples of the fruits of this new scientific field. However, at the same time, the ideas of genetics were extended to a number of human problems with disastrous consequences. Many leading geneticists at the turn of the century became part of the eugenics movement. Followers of eugenics believed that people were born with either superior or inferior genes. They believed that many of our social problems could be explained by the existence of people within the population with defective genes. They saw a whole range of problems as being due to simple genetic traits. These included poverty, criminality and even seafaringness.

These ideas took strong hold in this country during that period, and as a result of the lobbying of eugenicists a number of laws were passed which caused great harm. These included miscegenation laws passed in over 30 states which prevented the marriage of whites and blacks and, in a number of states, whites and orientals. Sterilization laws allowed the sterilization of people with low IQ's, of criminals and, depending on the state, other personality traits. These laws were still being implemented in certain states up until the 1970's. In 1924, the U.S. Congress passed the Immigration Restriction Act which greatly reduced the influx of immigrants from Southern and Eastern Europe. Eugenicists testified before Congress that the continued influx of immigrants was causing a deterioration in the genetic stock in this country.

Another example of the harmful effects of eugenics ideology was the case of pellagra. Pellagra was a disease found commonly among poor people in the South. Eugenicists, who tended to see everything in genetic terms, were convinced that pellagra was a genetic disease because it ran in families. In fact, pellagra is a nutritional disease due to the absence of a vitamin in the diet. That it was nutritional was discovered by Dr. Joseph Goldberg in 1915. However, so strong was the influence of the eugenicists that they managed to convince government policy makers of their view that pellagra was genetic and thus prevented appropriate treatment of the disease for 20 years. Tens of thousands of people suffered needlessly or died as a result of the influence of the eugenicists.

The most extreme example of the use of genetic ideas to harm and oppress people was in Nazi Germany. The extermination of millions of Jews, Slavs, homosexuals and mentally retarded was based in good part on arguments that these people were genetically inferior. However, it is important to realize for understanding the implications of our contemporary situation, that it was not the Nazis who first dreamed up these programs. The Racial Hygiene movement had existed in Germany for many decades before the Nazis came to power. As the eugenics movement in this country had many geneticists in it, the Racial Hygiene movement was dominated by scientists and doctors. Psychiatrists and others spoke of the "destruction of lives devoid of value" in the 1920's. These arguments were always couched in medical terms.

The example of Nazi Germany led to a revulsion after World War II at the consequences of the genetic theories of human problems and, for at least two decades, arguments of this sort were not received with favor.

However, beginning in the 1960's arguments reminiscent of the earlier period began to surface again. In the late 1960's and early 1970's, Arthur Jensen and others claimed new evidence that blacks were genetically inferior in intelligence to whites. Jensen's articles were read into the Congressisonal Record and were used as support of the arguments for ending compensatory education programs. The certain influence on racial attitudes, in general, on teachers and on the self-esteem of blacks cannot be measured.

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These arguments have been appearing in an era of explosive progress in the field of genetics over the last 25 years. The new genetic technologies again provide enormous benefits to this society. Screening techniques for human genetic diseases have made great advances and there may be much potential in recombinant DNA technology for developing new vacines and other beneficial products. At the same time, the ghost of eugenics is still with us. The idea of a genetic fix to solve society's problems is seen in numerous ways. I believe this committee recently heard of genetic screening programs in industry, which, while based on little hard scientific evidence, have the potential for discrimination against certain groups and a deflection of attention from the problems of industrial pollutants.

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These are only meant to be illustrative examples, not predictions. If the past is any guide, the dangers may well come from areas we cannot foresee at this point. My fear is that much of this may come about through what appears to be "progress" in medical research and medical treatment. In the same way that German doctors proposed sterilization and euthanasis for "medical" reasons, and that doctors' communication with prospective parents has led to the abortion of XYY fetuses, eugenics practices with dangerous consequences may well grow without our even being aware of it.

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Dr. Davis: "If one systematically did I.Q. tests on these kids as they became adults, compared them with their parents, it would make a great deal of difference, I think, whether they averaged five points less than their parents or 20 or 25 points less than their parents. I would think that kind of information would be worth trying to get, so parents could make their decisions as to whether they wanted to have that kind of child." Then Dr. Cederbaum: ". . . we should recognize that this is a form of problem and inperfection that parents should have a right to terminate, if such were technically available."

Why did not these scientists suggest systematically following up these kids to determine whether they became happy adults or whether they contributed to the welfare of their society?

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While we cannot help but be excited and hopeful about the prospects that gene therapy opens up for reducing human suffering, we cannot ignore the potential dangers which come along with it. In the past, those who have suffered at the hands of genetics have been those with the least power in this society. I have no qualms about describing Tay-Sachs or Cystic Fibrosis as medical problems which require a medical approach. I do have very serious questions about allowing doctors to make decisions that a lower IQ is a medical problem. There must be a clear-cut demarcation made between medical problems and issues which involve societal judgements.

Mr. GORE. Thank you very much.

Let me say in response to you and your colleagues who are suggesting further hearings by this subcommittee, we intend to have further hearings, and we welcome any suggestions that you and other members of the scientific community might have as to how we can better focus the inquiry and how we can make more progress. So, I invite all of our witnesses to do the same.

Do any of the witnesses on this panel disagree with the recommendation that we have some sort of governmental body, either an expanded advisory committee independent of NIH or a mutated President's commission or some governmental body, to focus our awareness of developments in this field and monitor them and explore the implications of the new discoveries?

Anybody disagree with that? I don't think we have had a single witness in the 2 days so far of hearings that does not support that or who expressed disagreement with that proposal. I will continue to ask witnesses tomorrow.

Dr. Beckwith, you talked about an idea at the end of your statement that I think is very close to something Dr. Zaner is saying. Dr. Zaner talked about the importance of developing a professional moral code among scientists in this field. It is a very intriguing suggestion. You discuss a specific mechanism that might be used as one mechanism to help develop that sort of code.

Did you see his suggestion in the same way I did, Dr. Zaner, that that may be a way to reach the goal?

Dr. **Zaner**. Indeed, I saw both suggestions that way: The sense of a local presence, the need for local presence with a greater public involvement. I am committed to the idea of not just multidisciplinary, as we academics call it, but a kind of group that involves different citizen groups, principally, first and foremost for educational purposes, and possibly to formulate effective kinds of suggestions, recommendations that might then be able to be put into practice, both on the local and national level.

Mr. **Gore**. Dr. Beckwith?

Dr. **Beckwith**. This is basically following up on I think something Dr. Shinn said earlier, which is that in general, it is the poorer and less powerful groups in society that have suffered from the negative effects of this work. Therefore, it is important for them to interact with scientists and politicians to affect these issues.

Mr. **Gore**. Yes. The Supreme Court has an interesting approach to issues involving racial discrimination that I want to use as an analogy.

When a question is raised involving discrimination against a group that has historically suffered discrimination, a different level of scrutiny is applied to the factual case. Strict scrutiny is the phrase often used because the historical record of how such questions have been dealt with in society is such that strict scrutiny, closer scrutiny is required.

I might extrapolate from your statement this morning a feeling on your part that the history of our civilization's handling of genetics might warrant a stricter scrutiny than is used where other sciences are involved.

Would you agree with that formulation?

Dr. **Beckwith**. I am not sure we need any more reasons than the ones offered by all of us this morning for observing that scrutiny. That would be one among many reasons.

Mr. **Gore**. All right.

Dr. Fletcher, you draw a sharp distinction between procedures that affect the somatic cells and procedures that affect the germ line cells. This distinction was drawn by other witnesses yesterday, and it seems to be a great divide, a very important distinction.

You further indicated in your testimony that there is a very well-developed, a highly developed, sensitive and mature body of ethics governing medical procedures closely similar to those that are contemplated when we talk of gene therapy on somatic cells, but in your opinion, there is an immature body of ethics not fully developed where procedures aimed at germ line cells are involved.

Dr. **Fletcher**. Yes, you put it better than I did, Mr. Chairman. I think mature and immature is very apt. Certainly bodies of ethics evolve and grow, and our ability to envision all the issues and to feel something like in control of the issues does grow.

I think that you can trace the history of the growth of ethical wisdom if you look at Dr. Nirenberg's appeal in 1967. He said that the ability to program cells was here but that the ethical wisdom to use it for the benefit of mankind was not here.

Mr. **Gore**. Yes.

Dr. **Fletcher.** Now, I used that statement like a text and examined the growth of ethical wisdom to use gene therapy medically on somatic cells, I think you can make the case there is sufficient wisdom in research ethics that has evolved in the last 25 or 30 years, a great deal of work and careful articulation has gone on, and a nationwide system of decisionmaking so to speak is there.

However, only an embryonic form of ethical wisdom has started to be offered on more complex genetic research. My colleague, Dr. Walters, offered thought experiments. I think that was well chosen. It is a cautious thinking of what conditions might or might not be advisible for the future of gametic correction. I think there is something like close to a quantum leap between somatic cell thinking and gametic cell thinking.

I am ready, I feel ready and confident that the people involved, researchers and physicians and the families involved, do have enough guidance to make those first decisions if the scientific basis is there. But not so for gametic corrections. A lot of work and thinking has to be done about that and I am relieved and glad we do have a lot of time.

If you notice I put this in a 50- to 100-year span.

Mr. **Gore.** Many of our other witnesses disagree strongly with that time estimate.

Dr. **Fletcher.** I know they do, but for wisdom to grow takes a lot more time than to grow cells.

Mr. **Gore.** Yes, that is right, but if I thought that we had 50 years before gametic surgery was going to be feasible and done, then I would feel better about our prospects for developing a mature body of ethics to guide decisions that will confront us out of that science, but I am afraid that the pace of this science is surprising everyone, even this year between the first and second drafts of the President's Commission new experiments took place that were shockers in the sense that they showed us how quickly the science was moving.

If one thought that gametic surgery was going to happen much more quickly, sooner, would it ever make sense for the scientific community to remedy the slow pace of this growth in the body of ethics compared to the fast pace in the hard science itself?

Everyone talks about the DNA safety episode as a success story. I think it was a success story. But in that case, there was a moratorium while the safety questions were fully explored and thoughtful people satisfied themselves that the worst risks that were discussed could be avoided.

Should we ever contemplate a moratorium on changes in the germ line cells until we can build up this body of ethics to help us make decisions on matters that are going to have long-term consequences?

Dr. **Fletcher.** It is an idea well worth discussing. The idea has merit. I am not saying I support it definitively but it is certainly something that should be at the center of the deliberations of any official body set up to discuss the future of gene therapy.

I can well envision many decades of discussion of the types of experiments that would be considered permissible to do with human sperm or ova and distinguishing those from impermissible types of experiments. Look at the history of the consideration so far beginning with fetal experiments in the mid-1970's. What the Ethics Advisory Board and the National Commission for Protection of Human Subjects did was to separate permissible from impermissible experiments.

But they did that in the context of a science that was really upon them.

I ask you to reconsider your timetable because my contention is that the science that would make gametic correction possible in humans would probably follow on a long period of observing the consequences of somatic cell therapy and not before. I see no reason, and have not been told by any scientist any reason for trying anything in the human gametes until the consequences of somatic cell therapy were well examined.

Mr. GORE. Dr. Walters just told us that this group in Europe has prepared a list of permissible germ-line cell changes; is that correct?

Dr. WALTERS. What they proposed, in approving a recommendation concerning gene therapy, was that a list of serious human diseases be prepared for which it would be appropriate to use somatic or germ-line gene therapy.

Mr. GORE. I see.

Dr. WALTERS. I don't think the list has been prepared, but I suspect that what the Parliamentary Assembly had in mind was a list of diseases that everyone recognizes as serious, for example, Tay-Sachs disease or sickle-cell anemia or thalassemia, where there could be no question about gene therapy being used as in enhancement technique.

Mr. GORE. You wanted to comment, Dr. Zaner.

Dr. ZANER. I did, Mr. Chairman, thank you.

On the point to which Dr. Fletcher was addressing himself, in some ways to persons having long concern with ethics it rings funny on the ear to ask about growth of ethics like one asks about growth in scientific knowledge. One has to have a context for this.

Suppose it were as you suggest possible that gametic surgery could soon be done, would we be able to grow in our moral comprehension and so on in time to be able to condone that kind of thing?

We have to realize first of all that public discussion, much less widespread professional discussion of moral phenomena is only very recent in our culture. There have been lots and lots of discussions of religious phenomenon, and so on, and not with the edge that it has today.

This is a relatively new development.

Mr. GORE. Since Nurenberg.

Dr. ZANER. Yes, I would agree. Since in the history of science which long understood itself as value-free, relegating the whole question of values elsewhere.

The discussions of these tended to be relegated to very small groups of theologians, philosophers, and others. One of the reasons I mentioned that brief history is that one of the important kinds of suggestions coming out of the experience of bioethicists working in medical schools for the last 15 years was a genuine widespread concern, moral concern for oneself, for one's progeny, and other folks and so on; second, with a great deal more concrete factual information for example about diagnostic techniques in utero, with a great deal more knowledge and understanding of what actually goes on in the name of science, I think it has been quite remarkable—at least in my experience and those I have talked with about this in this field—how rapidly a sense of moral conscience and information on that side can grow as well.

Mr. **Gore**. Yes.

I don't mean to be too optimistic about the thing. I do want to suggest that the point I was making earlier about the need for understanding moral issues in the context in which they actually occur needing all the information and knowledge that comes along with that, that we may be too pessimistic to think that we simply don't and will never have that kind of wisdom needed.

Mr. **Gore**. You know, the phrase, "the growth of ethics, the growth of the body of ethics," I don't think should sound strange in this context. I think one of the witnesses on the first panel had a pattern, drew a pattern, it may have been Father McCormick.

Dr. **Zaner**. Yes, it was.

Mr. **Gore**. He said the pattern is you have a value, a new technology, and then a new series of questions. In this case, you have a new technology which creates a whole series of new questions, and the growth of ethics would follow the following pattern, it would seem to me:

No. 1, inventorying the new possibilities that are created as the new technologies intersect with reality as we know it.

No. 2, assignment of probabilities to the inventory of possibilities, and ranking them accordingly.

And then No. 3, judging the probabilities against the values that we believe to be important, and then, No. 4, making some sorts of judgments about where those values are likely to be contradicted or violated, and that takes time.

It takes an enormous amount of time, and when this science is just thrown upon us, the number of new possibilities is quite large, and we can spend a great deal of time in hearings like this one inventorying the possibilities, and then we can spend time arguing about what probabilities to assign to different possibilities.

Then we find that it is not all that difficult, really, to agree on how some of these probabilities relate to the values that we share, but it does take time to anticipate them and to develop a body of ethics that is available for some of the more subtle judgments that researchers and doctors are going to confront, and given the history that Dr. Beckwith usefully instructs us to look at and learn from, there are possibilities of misuse of many of these potentials, and as a result I think it is important that the growth of ethics in this area keep pace with the new possibilities that science gives us.

Yes, Dr. Walters?

Dr. **Walters**. On the matter of a moratorium, I think it is worth noting that de facto there has been, so far as we know from the published literature, a moratorium on attempts at gene therapy in humans since Dr. Cline's experiments, and this seems to have grown out of a consensus within the biomedical community that the time is not yet ripe.

Mr. **Gore**. That is on somatic cells?

Dr. **Walters**. That is on somatic cells.

Mr. **Gore**. It is on all kinds, really.

Dr. **Walters**. Yes.

Mr. **Gore**. That is because of an analysis based on this traditional mature body of ethics that has grown up in medicine essentially, the risks and the benefits and all of the other judgments that are made did not, in the view of most, support the experiments that Dr. Cline began. He will be here tomorrow to talk about his view of that.

Well, I am not proposing a moratorium on gametic surgery. It is not a ripe question to use another Supreme Court analogy. It is a question that may become ripe pretty soon, though, depending on how quickly the technology develops.

Do any of you have views to share on the implications of gene mapping which we heard about yesterday, this development of a computerized library of all the information about the human genome? The knowledge in it is said to be doubling every 6 months. Within 2 years, they plan to have 400 street markers completely circumscribing the human genome, and then begin filling in the gaps between the markers to construct a complete blueprint eventually.

Do any of you care to discuss the implications of that? Dr. Beckwith?

Dr. **Beckwith**. As I stated earlier that the new gene mapping techniques will enhance tremendously the ability to detect a variety of genetic diseases that we can't detect now. That is going to be of tremendous benefit.

Mr. **Gore**. Yes.

Dr. **Beckwith**. However, I am also concerned about the relationship of gene mapping to areas of research dealing with human behavioral characteristics, where there have been claims that there are links between genetic characters and certain behavioral characteristics. To my mind, these reports have been scientifically very poor; but often, they have achieved a lot of attention and credibility.

I remember seeing a few years ago a couple of projects where scientists were using chromosome banding, which is an earlier technique preceding the newer techniques for looking at chromosomes in this finer way. They were trying to correlate various chromosome bands with IQ and race, and published a couple of abstracts on these claims that there was some correlation.

I think that was poor science, but it was also very dangerous. Now, I am concerned that with the availability of these more refined technologies, the same kind of things will happen with greater frequency. I don't have any solutions as to how to deal with that, because as I said, I think, that in almost every case, it has been poor science.

Mr. **Gore**. Yes.

Dr. **Beckwith**. Nevertheless, the results of such studies have attracted attention because they cohere with certain people's attitudes about our social problems.

Mr. **Gore**. Yes.

Dr. Walters?

Dr. **Walters**. The discovery of DNA in the 1950's already frightened us as human beings somewhat, because it seemed as if we were reduced to nothing more than DNA. I suppose what seems most frightening about gene mapping is that it simply carries this a step further and says not only in general, but these are the specific types of DNA that are in different parts of the human genome, but if we step back from this question and try to look at it in a rational way, it seems that gene mapping is an important next step if we hope to overcome some of these genetic diseases through gene therapy, so I think it is a very important development.

Mr. **Gore**. Let me ask you one question. We were talking about that European list. Does the list of permissible activities according to the European Parliamentary Assembly imply prohibition on those not on those not on the list?

Dr. **Walters**. I think that the European Parliamentary Assembly was drawing a line implicitly between the cure of genetic disease, which it wanted to approve of either through somatic-cell or germ-cell modification, and what it called artificially interfering with people's genetic inheritance.

Mr. **Gore**. Yes.

Dr. **Walters**. They did not specify clearly what they had in mind. They were trying to create a new right for the members of future generations——

Mr. **Gore**. Yes.

Dr. **Walters** [continuing]. Namely, the right not to have one's genetic inheritance artificially interfered with.

Mr. **Gore**. That is something that perhaps this new governmental body could discuss. I am not sure it is something that we would want to implement here.

Dr. Fletcher, you talked about putting this field firmly on a medical course. It seems to me that one of the things this new body might do in addition to simply keeping an eye out for pitfalls, it might also seek to identify opportunities and suggest ways to exploit opportunities, and when you describe a medical course, I am reminded of Mr. Skolnick's testimony yesterday, in which he said that genetic mapping will make possible a whole new area of preventive medicine, and that, it seems to me, would carry an ethnical obligation for our society to quickly and most fruitfully exploit that new opportunity.

Would you not agree?

Dr. **Fletcher**. I agree with that in principle, yes. When you raised the gene mapping issue, I had two thoughts. Certainly this knowledge about ourselves should not be proscribed. Each of us carries probably between, I have seen the figure debated, between 4 to 8—Dr. Williams said 20 lethal genes in our genome. I am not sure about that scientifically, but a number of lethal genes.

Human beings are curious about themselves genetically for good reasons, to try to prevent harm.

Mr. **Gore**. You are not proposing genectomies, are you?

Dr. **Fletcher**. No. But if there is a tremendous explosion of knowledge about ourselves in a negative sense, we find out where most of our lethal genes are actually located, if we don't have anything positive to offer ourselves or our children in the forms of therapy to do something about this, I do think that increased knowledge of ourselves genetically will be negative, will be depressing, and will tend to bind us up and make us look at human beings more negatively than we ought, so that I hope that the field of gene therapy grows and tries to keep pace with the ability to have more genetic knowledge and map the genes.

Mr. Gore. The example that was most instructive to me was a disease that is genetically based, and I can't think of the name of it, maybe some of you can help me out. It is an iron surplus. It is rather late in life, hemocomatosis, and in the terms of the example used, screening for that disorder could find a million cases among those Americans presently alive, a million people who will die prematurely albeit late in life as a result of that condition, the treatment for which is very, very simple, just become a regular blood donor, and it seems to me that if we acquire the ability to screen that out and treat those people, then at some point we as a society have an ethical obligation to exploit that opportunity, and a governmental body of the kind that has been discussed, I think, might be able to identify such opportunities, and suggest ways to exploit them, and have a positive role as well as just a technological role.

Dr. Fletcher. I agree that is constructive and creative, a goal-setting function.

Mr. Gore. Well, we have had a long hearing, and we have a third day tomorrow, and a very full day of witnesses tomorrow on this same subject. I think the testimony of this panel has really been unusually good, and I would like to thank each of you for your participation and your contribution here this morning. We appreciate it very, very much.

With that, the hearing will come back into session tomorrow morning at 9:30 in this room. For now, we are adjourned.

[Whereupon, at 12:15 p.m., the subcommittee recessed, to reconvene at 9:30 a.m., Thursday, November 18, 1982.]

HUMAN GENETIC ENGINEERING

THURSDAY, NOVEMBER 18, 1982

House of Representatives,
Committee on Science and Technology,
Subcommittee on Investigations and Oversight,
Washington, D.C.

The subcommittee met, pursuant to call, at 10:36 a.m., in room 2318, Rayburn House Office Building, Hon. Albert Gore, Jr. (chairman of the subcommittee) presiding.

Mr. Gore. Over the last 2 days, this subcommittee has engaged in a fascinating exploration of the scientific, religious, and ethical issues inherent in human genetic engineering. From our discussions with scientists, we have learned that the scientific capability to manipulate the human genome is developing far more rapidly than we or they had originally anticipated.

Witnesses during the first day of this hearing estimated that within 2 years a basic map of the complete human gene structure will have been compiled and that actual genetic engineering on humans will be possible within 5 to 10 years.

Yesterday, the subcommittee heard from a number of religious leaders and ethicists regarding their hopes for and concerns about the new technology. It was abundantly evident from our session yesterday that enormous religious and ethical issues are raised by human genetic engineering. It was also evident that at the present time most of those issues remain to be resolved.

Today we move to the third step in the subcommittee's present consideration of the human genetic engineering controversy.

Today we will consider where we as a society ought to be heading with human genetic engineering and what social policy perspective we should take toward the science.

For example, do we have a societal obligation to engage in genetic research and engineering to cure diseases? Are there certain directions that ought to be avoided and certain areas that should not be explored? Should we prohibit genetic engineering for certain purposes? What sort of oversight mechanisms should exist?

Throughout the first 2 days of our hearings, it has become clear that our existing social and political institutions are ill equipped to deal with the dramatic and rapid advances now being made in human genetic technology. It has also become clear that some new form of oversight mechanism will be necessary to review the future development of this science and its many implications.

This morning, we will hear from scientists, sociologists, philosophers, and others who have expressed opinions on the future course of human genetic engineering. Our first witness today will be Dr. Martin J. Cline from the UCLA Medical School.

Two years ago, Dr. Cline attempted to treat two individuals who suffered from a severe blood disorder through gene therapy. Dr. Cline's attempted treatments, however, were unauthorized, and Dr. Cline was penalized by the scientific community.

Dr. Cline's case is an example not only of one scientist's view of what may be possible with human genetic engineering, but also of the way in which existing institutional mechanisms responded to a violation of existing guidelines. Dr. Cline's case may be instructive, and his opinions will be valuable.

With our witnesses today, we will explore various concepts and proposals for future oversight mechanisms. It is not yet clear either what shape any new body should take or what authority it should have. Through our discussion today, however, we hopefully will achieve a better understanding of what will be needed in this regard.

I would like to thank all of our witnesses for coming. I would like to particularly thank those who have had to stretch their schedules and change their plans because of the unanticipated delay in our starting time and because some of our witnesses who were kind enough to come and are participating on the last panel have to leave relatively early.

I want to tell all of the witnesses today that we are going to attempt to move at a somewhat faster pace today then we have in the past, so that we can finish expeditiously.

I would like to call now our first witness, Dr. Martin Cline, professor of medical oncology, University of California School of Medicine, in Los Angeles.

Dr. Cline, welcome. We are delighted to have you appear here today. Without objection, the entire text of your prepared statement will be included in the record in full, and if you care to summarize any portions of it, feel free to do so.

If you wish to present it in toto, that is certainly acceptable.

STATEMENT OF MARTIN CLINE, M.D., PROFESSOR OF MEDICAL ONCOLOGY, UNIVERSITY OF CALIFORNIA SCHOOL OF MEDICINE, LOS ANGELES, CALIF.

Dr. Cline. I gather, Congressman Gore, in the first 2 days of these hearings, that the distinction between what I shall call genetic engineering and gene therapy has been quite clear. I will summarize my concept in a sentence or two.

Mr. Gore. Let me say the distinction between therapies directed at somatic cells and therapies directed at germ line cells has been made, adequately, I think. The terminology which you use in your statement may not be universally accepted.

As I understand your terminology, you seek to supply the phrase "gene therapy" to those procedures directed at somatic cells and genetic engineering to other procedures, including those which are directed at germ line cells. Is that essentially correct?

Dr. Cline. That is correct.

Mr. Gore. That distinction, as expressed in that vocabulary, I want to think about. I am not sure that is universally accepted, but for purposes of your statement, if it is clear that is what you mean, then please proceed.

Dr. CLINE. Let me restrict my remarks to gene therapy in relation to putting new genetic information into somatic cells, where that information will not be transmitted to the offspring of the recipient.

By way of introduction, I would like to present a brief clinical history of a young girl. I can show her on the single slide that I brought.

The young girl is seated in the center. On her left is her physician. Behind her is her mother. Obscured in the background is a young Italian physician somewhat less formally dressed than his American counterpart might be.

At the time this picture was taken this girl was about 15 years old, although she had the stature of a girl of roughly a 12-year-old. She had not yet entered puberty, a feature that would be a fairly typical manifestation of her disease. Since birth, she has had a form of hereditary anemia called thalassemia major. It is a severe, destructive type of anemia for which there is inadequate compensation by the patient's bone marrow cells.

Had she not received no transfusions, she would have had gross deformities of bone as a consequence of the bone marrow's attempt to compensate for this severe anemia. The result would have been rather grotesque features. However, from early childhood, she had received transfusions which had suppressed her own bone marrow activity. These had been administered mainly by that physician I see there on the left.

Mr. GORE. You are talking about a blood transfusion, yes?

Dr. CLINE. That is correct. In summary the patient was maintained for 15 years by blood transfusion. She, of course, suffered some consequences of this treatment. A distinct iron overload accompanies each transfusion. Each night, when the patient went to bed, she would sleep with a needle stuck beneath the skin attached to a motor-driven system which infused a drug slowly over the course of the night. The objectives of this procedure were to get rid of the excess of iron in her body. The infused drug would allow her to excrete the iron in the urine. Her life was bound to this type of constant medical management.

The therapy was, however, not totally sufficient in that she did have significant iron overload of her tissues. Her late puberty was one manifestation of this overload with, iron deposition in a variety of glands. This phenomenon is quite typical of this disease.

But more important is a deposition of iron in the heart with eventual manifestations of either abnormal heart rhythm or heart failure the patient had already had several episodes of abnormal heart rhythm.

She was judged to be in a fairly advanced stage of her disease and had, with current level of medical technology, a limited life expectancy. The cause of this disease is well defined. In this patient, it is known there is a deletion of some of the genes involving production of hemoglobin, the major oxygen-carrying protein of red cells. She inherited this from her parents. Although she comes from Torino, her parents are Sicilians; reflecting the wave of migration that has moved people from the south of Italy to the factories of the north.

The cause of her disease was, therefore, quite clearly defined. The manifestations have been well documented over a long period of time, and there exists the possibility that eventually insertion of a normally functioning hemoglobin gene could ameliorate and possibly eventually cure a disease like this.

About 2 years ago, we undertook what we envisioned as a series of investigations which we thought would span approximately a decade. In these we would apply sequentially one and then another strategy of gene therapy.

The strategy we chose to use at that point in time was to remove a small amount of her own bone marrow—by a standard procedure performed in all modern hospitals removing about an ounce of bone marrow.

These marrow cells were incubated with two genes. One, was the human beta globin gene that was defective in her cells; the other gene was one which I have chosen to call the selective gene which would give to any recipient cells or target cells an advantage in proliferation.

The genes were precipitated to form a complex that would look roughly like microscopic salt. Her bone marrow cells were incubated for a period of time with the precipitated genes and were thereafter returned to her intravenously, with the expectation that some of the cells would eventually home to the bone marrow and begin proliferating.

What were the envisaged obstacles or problems that we anticipated with inserting new genetic information into the marrow cells? First, of course, one would have to have the genes get into some of the early cells of the bone marrow and stay there at least transiently.

Next, the returned bone marrow cells would have to circulate, and at least some of them would have to return to the patient's marrow and begin proliferating. Some of these cells would have to carry the hemoglobin gene at least transiently, and would have to express this gene at some level which would be useful to the patient, to be useful, neither too much nor too little hemoglobin would have to be made.

Finally, the newly inserted genes should produce no aberrations, or damage to the functions of the cells.

In these initial studies we hoped to learn two things. First, we hoped to learn whether such cells carrying new genes could successfully return to the bone marrow and begin proliferation; that is, would we see evidence of the acquisition of new genes even transiently.

The second and most important thing we hoped to learn was whether there was any toxicity associated with the procedure. We anticipated from extensive animal experimentation that there would be no toxicity; however we knew that whenever one introduces new genetic information into cells, there is the possibility of aberrant expression.

We were concerned about this possibility, and thought that the information in relation to toxicity would probably require several years to accumulate.

We felt, in addition, that the initial studies should be in patients with a limited life expectancy.

The objectives of the research were well defined. Requirements for the initiation of research in man were knowledge of the behavior of inserted genes in animal model systems of bone marrow transplantation, and observations of potential toxicity in animals for prolonged periods of time.

What are the ethical considerations that relate to this type of gene therapy? In my opinion, there are no ethical considerations beyond those that relate to any types of novel human experimentation in man.

We have used many different biological agents to treat human diseases over many decades. I think DNA is really no different in this regard. There are obviously, many things to learn about DNA: Its potential toxicity, its mechanism of integration, the modulation of its expression and so forth; however, I see no peculiar or novel types of ethical considerations in this type of gene therapy.

What sort of restrictions or legislation do we need in relation to this type of gene therapy? In my opinion, none beyond those that we already have in force relating to any type of experimentation in man.

Thank you.

Mr. GORE. Does that complete your statement?

Dr. CLINE. That completes my statement.

Mr. GORE. Very good.

It is not our place to judge you, Dr. Cline, nor is that our intention or purpose. It is of interest to us how you were judged by the mechanisms that are currently in place, and how that mechanism is working. Because of the special characteristics of genetics—I started to say genetic engineering—and because the line of demarcation between procedures directed at somatic cells and procedures directed at germ line cells has only recently become clear in the minds of those attempting to develop and further the body of ethics which surrounds these procedures.

You were adjudged by the review mechanism in place. Let me review a little bit of that with you. It seems that one of the things that troubled them was that you did not inform the human subject review committees either at UCLA or at Hadassah that you planned to use recombinant DNA.

Is that a fair or unfair statement?

Dr. CLINE. I think that is a fair statement.

Mr. GORE. That you did not inform them.

Dr. CLINE. That is right.

Mr. GORE. Should you, in your opinion, should you and other doctors in your position inform committees?

Dr. CLINE. Yes. The answer is yes. One should put this statement in perspective or in its proper context.

Mr. GORE. That is one of our principal purposes, so please do.

Dr. CLINE. At the time of the study, I considered the initiation of those studies to be quite important and quite a serious matter. I actually considered the recombinant form in which those genes were inserted to be a relatively trivial aspect of the study; the reason being that it was well-known at that time that individual genes, whether or not they are linked together as recombinants, become recombined once they enter cells. There is a biologic reality relevant to recombination of these molecules, whatever other laws might exist. The newly inserted genes do become recombined in situ in the cells. The use of the recombinant molecules was an error in the way I used them, but I considered their use at the time to be a relatively unimportant aspect of the whole procedure.

I thought the aspects of the studies in relationship to patient management, selection of the patients and so forth, the way the initial studies were designed to obtain scientific information, were paramount; I actually considered the latter recombinant aspects of the study to be rather trivial in nature.

Maybe that is an unfair way of saying it, not trivial, but not very important.

Mr. GORE. And you never received approval from any biosafety committee.

Dr. CLINE. No, that is not accurate.

Mr. GORE. You never received approval to use recombinant DNA?

Dr. CLINE. I had received approval to carry out the general procedure which I just outlined from a human safety review committee at Hadassah Medical Center.

Mr. GORE. Based on their misunderstanding that recombinant DNA was not to be used.

Dr. CLINE. Based on the understanding that the genes were separated at that time.

Mr. GORE. They gave you approval at a time when they thought you were not going to use recombinant DNA?

Dr. CLINE. That is right.

Mr. GORE. And in your mind, the use of recombinant DNA instead of——

Dr. CLINE. Separated genes.

Mr. GORE [continuing]. Separated genes was an incremental step that you did not feel to be of sufficient importance to warrant clarifying the matter in the minds of those who were charged with approving or disapproving the procedure?

Dr. CLINE. That is correct.

Mr. GORE. I think it is important to establish and support the authority of committees like this. It is clear that individual doctors and scientists will come into conflict with the authority wielded by such committees, but it does seem to me important that they have that authority and that the wielding of that authority be supported.

Let me ask you about a question in your prepared statement. On page 15, you say, "The inherent dangers of introducing DNA into marrow cells or liver cells are probably no greater than those of many of the new drugs that are introduced annually into clinical medicine."

How do you know that?

Dr. CLINE. That is how I spend my life, Congressman. I am a cancer chemotherapist by trade, and treat patients with malignant diseases with a variety of drugs, some well established and some newly introduced.

Mr. GORE. Upon what evidence do you base this statement?

Dr. **Cline**. I see many drugs introduced that have considerable toxicity to cells and to patients. Would you like me to list some drugs?

Mr. **Gore**. No, that is a matter I am sure no one could dispute or would dispute, but the comparison of one to the other implies a base of knowledge not only on the use of the drugs, but also a base of knowledge on the introduction of DNA from which you can make a comparison one against the other.

You have made the comparison that the inherent dangers of introducing DNA into marrow cells are probably no greater than the inherent dangers of introducing many of the drugs that are annually introduced.

Dr. **Cline**. I think that is probably accurate.

Mr. **Gore**. Well, "probably"?

Dr. **Cline**. That is why I said "probably." There is still imprecise information with regard to DNA. It has only been introduced into a relatively limited number of living animals and those of only one species, so our knowledge in this regard is incomplete.

The theoretical dangers of introducing DNA into cells are those of introducing the new DNA into, undesirable sites that can activate genes that are normally quiescent. Potentially one might thereby either damage the cell or change its properties so it behaves like a malignant cell. These are the theoretical considerations of insertion of new genetic information into higher organisms.

One can perform certain calculations based on the number of molecules one introduces and their chances of inserting, near genes that are of critical importance.

The statistical probabilities of doing damage are small, but they probably exist. As I say, our knowledge of this area is still imprecise and is thus far restricted to studies of mice.

That is why I said, "probably." I do know of many drugs introduced annually into clinical medicine which do lots of harm.

Mr. **Gore**. We heard testimony yesterday indicating there is a relatively well developed and mature body of ethics that supports and surrounds judgments that are required to be made by doctors with respect to traditional treatment modalities and that that body of ethics is probably directly relevant to gene therapy directed at somatic cells.

We heard also that there is an immature, not well defined body of ethics that is beginning to grow around the use of genetic therapy techniques or genetic engineering techniques, if you will, that affect germ line cells.

I get the impression that in your mind you believe that the reaction elicited by your experiments came about in part because of a confusion between those two and that there was a vehement response that would not have been justified by the traditional body of ethics because of a real concern spilling over from the concern generally felt about genetic procedures that are more presently viewed in the context of germ line cells.

Dr. **Cline**. That is very well stated, Congressman.

Mr. **Gore**. Now, let me move from that to say that many of the witnesses who have commented on your case have said in very blunt terms that the problems they had with what you did really arose from this well-developed mature body of ethics surrounding treatment modalities.

Do you want to respond to that part of it?

Dr. CLINE. Yes. Let's put it in the context of the traditional ways we do clinical investigations in man: The decisions about when one initiates studies in man is not always clear cut.

Our recent scientific history indicates that first we do extensive studies in animals. We get information in relation to efficacy and toxicity in animals, and then we apply new modalities of therapy cautiously. We may apply them earlier when we deal with lethal diseases for which there are no good alternative therapies.

We apply the therapies more slowly in diseases which are susceptible to treatment by conventional therapy. I have spent most of my professional life dealing with lethal diseases, malignant diseases in particular.

I think I have a fairly good understanding of our traditions of instituting new therapies where we begin by exploring toxicities, drug distribution and so forth.

I think most of the outcry—against the genetic experiments—arose for two reasons; First, because it involved genes, and there was—and is—some confusion between gene therapy and true genetic engineering; the second is much of the outcry came from basic scientists who did not really understand either the process of clinical investigation nor how one initiates new therapies in lethal diseases.

Basically, much of the outcry was based on ignorance of the process of clinical investigation and ignorance of the details of the experiments that had preceded these initial studies.

Mr. GORE. Now, you speak of the experiments that had preceded these studies or attempted treatments.

It was my understanding—it is my understanding that it was only last month that the first successful gene transfer in laboratory animals was successful. Is that correct?

Dr. CLINE. No, that is not quite accurate. I think we were the first to describe successful transfer of genes in living animals. It was published in April 1980, in Nature, where we described putting genes for drug resistance into the bone marrow cells of mice. In those studies, which at the time of the clinical studies had been on going for 2 years, several hundreds of mice were examined, using two different selective genes. There was a fair background of information in gene insertion in bone marrow cells of animals. I will be happy to supply you with information on that.

Mr. GORE. That would be helpful if you could.

I have one more question on this.

Others expert in the field have talked about the premature nature of the experiment, in their opinion, and one basis for the charge was that no successful experiments akin to this procedure had been conducted——

Dr. CLINE. May I interrupt at that point, so we don't lose that thread?

In fact, the experiments were quite successful on animals. With one of the genes we had quite a high frequency of successful—and let me say stable—introduction of drug-resistance genes, and I might say that observation was subsequently reconfirmed in other laboratories.

Using another gene, the gene was less stable and the percentage of, let's say, successful takes, was lower.

So the animal experiments were quite successful in that regard.

You also have to realize we had limited expectations of what we wanted to achieve in the first human studies. We wanted to learn, two things. We wanted to know whether we could get marrow cells containing these new genes to home and proliferate so that we could detect the genes.

That is the first thing we wanted to know. Second, we wanted to know if there was any toxicity. We felt we would obtain clear answers to both of these questions.

Mr. GORE. Did your set of limited expectations include any expectation that patients might be benefited?

Dr. CLINE. We thought that it was highly unlikely that we would introduce the hemoglobin gene in a manner in which it would be stably inserted and functional. We thought the chances of that occuring were exceedingly remote.

We anticipated that eventually we would succeed, but that "eventually" would cover studies over a number of years.

Mr. GORE. Now, it is a matter of some significance whether or not there was any expectation that the patients would be benefited.

Dr. CLINE. Well, I think the chances of benefit, were less than 1 in 100.

Mr. GORE. As much as 1 in 100? That high?

Dr. CLINE. Well, one can't really be precise if it is 1 in 100 or 1 in 1,000 or 1 in 10,000. I don't think there is any clear way of defining that difference.

Congressman, perhaps you should understand that patients with fatal diseases who are the subjects of initial experimentation—let's take a patient with cancer and the introduction of a new drug. The chances that that patient will be benefited by the use of the agent are probably less than 1 in 100 as well.

Mr. GORE. Or even less.

Dr. CLINE. Surely.

Mr. GORE. I would like to recognize my distinguished colleague from Florida, Congressman Bill Nelson.

Mr. NELSON. Thank you, Mr. Chairman.

Given, Dr. Cline, the successful experiments that have been conducted on mice that you pointed out, do you think another effort to treat humans suffering from blood disorders should be undertaken?

Dr. CLINE. Yes, I do.

Mr. NELSON. Given that thrust, on page 13 of your testimony, it states:

> In certain cases, it should be noted that ethics committees, because of understandable conservatism and caution, delayed the introduction of innovative treatment that may help patients who are alive today and caught in the grip of an overwhelming disease.

Does this imply that you think that the ethics committees are unnecessary?

Dr. CLINE. No, it does not. I was just stating what I believed to be the fact. They—the committees—sometimes do delay such therapy.

Mr. NELSON. Then you don't think gene therapy should be just left to the physician alone involved?

Dr. CLINE. Oh, no. My point was that I don't think gene therapy of this sort represents any unique departure from human experimentation. I believe it should be subject to the same controls that govern any experimentation in man, but no unique controls.

Mr. NELSON. Can you tell us about the outcome of the treatments 2 years ago? Are the 23 women still living?

Dr. CLINE. Yes, they are, and they are in very much the same condition in which I found them. The patient in Israel, a young lady who suffers from severe episodes of heart failure, has had repeated episodes of heart failure since then, but she is still alive.

The saddest thing to me is I can't really tell you the outcome of the other aspect of the experiment which is whether genes were transiently inserted and circulated. I simply don't have that information.

Mr. NELSON. The Italian patient you are talking about?

Dr. CLINE. I don't have the information on either of the patients. My ability to carry out those studies was, let me say, severely curtailed shortly after the studies were performed.

Mr. NELSON. Was there an alternative treatment that had likely success when you made the choice to conduct the medical procedure that you used?

Dr. CLINE. At that point in time, and still, today, supportive therapy exists which consists of: One, blood transfusions to replace the blood that the patients marrow does not make and two, what is called chelation therapy, utilizing a drug which binds the excess iron. Chelation therapy is generally not wholly successful, and the iron deposition leads to a failure of a variety of organs.

Unless something dramatic happens the young lady in Israel will probably die within the next few years. Probably the girl in Italy will live a few years longer unless we come up with something else in the next few years.

Mr. NELSON. Insofar as you know, none of those alternative treatments have been undertaken?

Dr. CLINE. The supportive treatments, the transfusions and chelation therapy are being used in the young Italian girl, transfusion alone is being used in the Israeli girl.

Mr. NELSON. With those alternative methods used there is no way to measure whether or not there was any success in your method?

Dr. CLINE. No. We simply don't know the answer, whether it was successful or not. Very regrettable.

Mr. NELSON. You said in your testimony that public concern about gene therapy should be assuaged by a better understanding of the nature of that therapy and a realization it doesn't represent a radical departure from previous medical intervention to treat disease.

Tell me what you think about the public's confidence in science when physicians undertake unauthorized experiments?

Dr. CLINE. Well, I think the public's opinion is shaped very much by the media. I can't speak for the whole public, but I think probably a variety of views prevail. Some of the public have no interest at all and others are frightened by it. And others foresee the potential for benefit.

Mr. GORE. Will my colleague yield?

Mr. NELSON. Certainly.

Mr. GORE. I don't mean to joust with you, but the statement is that the news media is somehow responsible. In this case, what is responsible is your own colleague's——

Dr. CLINE. I didn't say responsible. I was asked how public opinion is shaped and——

Mr. GORE. Well, the question was, what happens to the public's confidence in science as a result of unauthorized experiments and your own committee at UCLA turned down this application?

Dr. CLINE. But only later.

Mr. GORE. Because you went ahead while it was pending before receiving action by them. That is not their fault.

Dr. CLINE. I had support by another committee, though.

Mr. GORE. For using recombinant DNA?

Dr. CLINE. No, not that.

Mr. GORE. You went ahead without any approval from one of these review committees and when they did review it, they turned it down. The NIH reviewed it. They will testify later about a number of topics, but it just seems to me that my colleague's question is a fair one, because the public's view of science is changing rather dramatically.

We have in this country always looked to science as a source of great hope and salvation and a source of solutions for many, if not all, the problems that we face.

There is a growing feeling on the part of many that our reach is exceeding our grasp in too many instances and we are acquiring powerful new tools and not exercising the care and wisdom necessary to wield them carefully, and I think that the responsibility of individual scientists in this profession is going to grow, must grow if the public's confidence in science is to be maintained as it must be.

And where the consensus in the scientific community is as strong as it was in this case, then it is hardly the news media that is the reason for the public wondering whether or not stricter controls are needed.

I will give you an opportunity to comment. I thank my colleague for yielding.

Dr. CLINE. I guess I would make one comment, Congressman, and that is, advances in science are generally not made by consensus.

Mr. GORE. Well, certainly the history of science would bear that out, and judgment calls are difficult for those in your profession, let alone those of us outside of it, and as I said, it is not our place to judge you, but your profession has in this case.

Mr. NELSON. Dr. Cline, what criteria would you suggest to evaluate the desirability of human experiments that would involve genetic engineering?

Dr. CLINE. I would divide them into two separate categories. I would rather arbitrarily call them gene therapy and genetic engineering. By gene therapy, I would mean the insertion of new genes into somatic cells. Not into germ line cells, so the new information is not passed on to any of the progeny.

I believe that we already have regulations in place for dealing with this type of innovative treatment, and I don't believe any new ones should be put into place.

In terms of what I have chosen to call genetic engineering—insertion of new genetic information into embryos or into adults in a way in which it would get into the germ line and be passed on to future generations, I believe there should be no restrictions and regulations in regard to animal experimentation.

I believe—I think Dr. Grobstein used the word moratorium—on any studies in regard to human embryos until we have sufficient information from animal studies to understand what the likely outcome will be.

I think you are probably aware that with the possibilities of in vitro fertilization that it would be possible to conduct experiments on human embryos similar to those that have already been described for mouse embryos.

I guess my feeling is we shouldn't do those at the moment until we really understand the animal systems.

Mr. NELSON. Thank you, Mr. Chairman.

Mr. GORE. Several witnesses have supported the establishment of a new government body to monitor and review the new developments that are coming in this field and focus our awareness on the implications of these new developments and periodically report to the Congress and I suppose advise the RAC at NIH. What is your view of that recommendation?

Dr. CLINE. I wonder if I could read a very brief excerpt from an essay.

Mr. GORE. It sounds like you anticipated that question.

Dr. CLINE. Well, others brighter and more able than I anticipate it.

I would like to read you a very brief statement from "The Medusa and the Snail," by Lewis Thomas. [reading]:

> The easiest decision for society to make in matters of this kind is to appoint an agency or a commission or a subcommittee with an agency to look into the problem and provide advice. And the easiest course for a committee to take when confronted by any process that appears to be disturbing people or making them uncomfortable is to recommend that it be stopped, at least for the time being. I can easily imagine such a committee composed of unimpeachable public officials arriving at the decision that the time is not quite right for the further exploration of the transportation of genes, that we should put it off for a while, maybe until the next century, and get on with other affairs that make us less discomforted.
>
> Why not do science and something more popular, say how to get solar energy more cheaply or mental health. The trouble is, it would be very hard to stop this line, once begun. There are, after all, all sorts of scientific inquiry that are not much liked by one constituency or another and we might find ourselves with included rosters, panels, standing committees, set up in Washington for the appraisal and then the regulation of research.

And so forth.

I guess my own view is that we do need some mechanism of oversight. I would have to say honestly that I don't think it will be very effective for two reasons. One is that whatever laws we might pass, I think the laws of nature are immutable.

The second is that that I think man has inherent inquisitiveness that one is not going to be able to regulate. Whereas we might be able to pass laws for the United States; I don't think we can do so for the rest of the world. If these lines of research are not pursued in the United States, then they will be pursued in Japan or Germany, and so forth.

So my own view is that almost inevitably we will set up such committees, but in the long run, I don't think they are going to be all that effective.

Mr. **Gore**. Well, let me say that no one has proposed stopping research in this field. You in your prepared statement say that the question is how we chart the course. I would add to that the question of who will chart the course. Will it be individual researchers, without relation to the body of ethics that we hope to build in this important area, or will it be some conglomeration of people with judgments informed by systemic inquiry into the implications of this new research?

Dr. **Cline**. May I pose a question to you, Congressman?

Suppose you had a child of 13 who was suffering from some incurable illness. Would you rather have someone like myself, presumably knowledgeable in clinical medicine, who has spent his life in caring for patients, making the judgments about what should be done next in the management of illness, or would you rather have a balanced committee composed of some professional people and lay individuals and lawyers making the judgment?

Mr. **Gore**. I am used to asking the questions, not answering them.

Let me depart from that practice and attempt to give you an answer.

I would, of course, advise anyone to rely upon the judgment of the physician chosen to exercise principal support for the care of the patient, be it a loved one or anyone else.

I would hope that that individual physician was himself or herself making judgments that bore reference to the best science available and was not an individual who would recommend a procedure so experimental as to have no known chance of benefiting my child whatsoever.

Dr. **Cline**. And you would also take the view that if the chances of benefiting the child were exceedingly remote but that one might learn something that might benefit another individual afflicted with the disease, that that experiment should not be done?

Mr. **Gore**. Your question is in the form of a compound sentence?

Dr. **Cline**. Yes, I'm sorry. I can break it down into the simpler component parts.

Mr. **Gore**. And it includes two elements. One is the hope that others later on might be benefited. The first part is remote chances of success.

There is a difference in my view between remote chances for success and no known chances whatsoever of success.

It is that distinct; if I understand the case accurately, that really turned the judgment of your peers in the other direction, and so if there was a remote chance and others would be benefited, I might well make the judgment that many thousands of persons make every year.

If, however, there was no known chance and no accurate quantification of the risks, then I would say no.

Mr. **Nelson**. Would the chairman yield?

Mr. **Gore**. Yes.

Mr. **Nelson**. I think we are drawing an example here that it is an either/or situation, either it is the inquisitive inventive physician or it is the conservative committee that is impeding progress and the ideal is not in that case of extremes, the ideal is that you have a community of peers who are inquisitive and inventive that are trying to apply some standards.

When we thought the world was flat, that was the conventional wisdom, but how do we as policymakers and lawmakers try to encourage the inquisitiveness?

Mr. **Gore**. Yes.

Mr. **Nelson**. An inventiveness in the peer committees.

Do you have any comment on that?

Dr. **Cline**. No; I think you have summarized what would be the ideal situation and one which we should strive for.

Mr. **Gore**. I would hope that any new governmental body set up to develop a better understanding of the implications of this new science would also inventory the positive opportunities for applying these new discoveries.

For example, the opportunity to develop new preventive medicine treatment modalities can go out of gene screening and some of the matters that you have discussed.

We are going to have to move on. Let me just ask you; you have made some very important statements in the latter part of your testimony about the future developments in this field. I think they are extremely valuable. You fully anticipate that doctors will be confronted with the decision about whether or not to eliminate disease like thalassemia for all succeeding generations, and I think by showing the picture of that patient on the wall, you have posed the dilemma that doctors in the future, perhaps the near future, will be posing to review committees throughout this country and elsewhere in the world, and I found that portion of your statement extremely interesting.

I wonder, could you give us for the record the consent forms that were used in these experiments?

Dr. **Cline**. I can provide them. I don't have them with me.

Mr. **Gore**. If you would do that, we would appreciate it. And on a later panel a representative from the NIH will testify about this, among other matters.

[The material referred to follows:]

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DEPARTMENT OF MEDICINE
UCLA SCHOOL OF MEDICINE
CENTER FOR THE HEALTH SCIENCES
LOS ANGELES, CALIFORNIA 90024

February 3, 1983

Mr. Steve Owens
Committee on Science and Technology
U.S. House of Representatives
Rayburn House Office Building, Suite 2321
Washington, D.C. 20515

Dear Mr. Owens:

At your request, I am enclosing a copy of the consent form entitled "Informed Consent for Experimental Gene Insertion and Autologous Bone Marrow Transplantation in Thalassemia" to incorporate into the transcript of the human genetic engineering hearings that took place last November.

Sincerely,

Martin J. Cline, M.D.
The Bowyer Professor of
Medical Oncology

MJC:gd

Encl.

INFORMED CONSENT FOR EXPERIMENTAL GENE INSERTION AND AUTOLOGOUS BONE MARROW TRANSPLANTATION IN THALASSEMIA

I understand that I have severe thalassemia. Thalassemia results from an abnormality in one of my genes which was present at birth. A gene is a component of all cells that determines heredity. I understand that there is no currently available treatment that will cure this disease but that available standard treatment can make me more comfortable and may prolong my life.

I understand that because there is no known cure of this disease, I agree to undertake these highly experimental treatments that involve (1) removing some of my bone marrow; (2) treatment of the removed bone marrow with 2 genes for a period of several hours followed by re-injection of the bone marrow into one of my veins; (3) the taking of a drug, methotrexate; (4) overnight observation after bone marrow injection, then weekly examination and taking of blood for at least 3 months.

It has been explained to me that two genes will be used in this experimental procedure. One is a gene from the Herpes virus; the other is a human gene for one of the components of normal hemoglobin. I UNDERSTAND THAT THIS GENE INSERTION HAS NEVER BEFORE BEEN PERFORMED IN MAN.

The possible complications of each of these procedures have been explained to me.

I consent to having 10 ml (about 2 teaspoonsful) of bone marrow removed through a needle from my hip bone at monthly intervals or more often if necessary to improve blood production. A single bone marrow may not work and several may be necessary. I understand that although complications of this procedure are rare, they do include (1) allergic reaction to the local anesthetic used to numb the skin and bone; (2) bleeding at the site where the bone marrow is obtained; (3) infection at the site where the bone marrow is obtained. Bleeding, if severe, would be treated with blood transfusion, and infection with antibiotics according to the judgment of the attending physician.

I consent to receive my own bone marrow by intravenous injection after it has been treated in an effort to supplement the gene for sickle cell disease with two genes. I understand that there is a risk of infection whenever bone marrow is taken out of the body and put back in. I understand that cells with new genes may not function properly and that there is an unknown risk that they could give rise to cancer. I consent to receive treatment for infection and treatment for tumors in the unlikely event they arise from treatment of my bone marrow.

I consent to taking the drug methotrexate in doses prescribed by my physician. This drug has not been used before in thalassemia.

...

I understand that this drug can cause anemia, low white cell counts with infection, low platelet counts with bleeding and damage to the digestive system including mouth ulcers, bleeding, and diarrhea. I understand that these complications are usually preventable if my blood counts are followed closely (usually at weekly intervals).

I consent to receiving blood transfusions as necessary to treat what my doctor considers to be a dangerously low red blood cell count. I understand that transfusions carry the risk of hepatitis with jaundice and liver damage.

I understand that all of the possible complications of this procedure can be mild or can be severe and even lead to my death. I understand that gene transfer is an experimental procedure, that has not previously been done in humans, the benefits of this procedure, if any, are uncertain and that in spite of gene transfer my condition may worsen. I have had adequate opportunity to discuss with my physicians the purpose and hazards associated with this procedure and am satisfied with this discussion. I understand that my rights as an experimental subject include my free and voluntary right to withdraw from this study at any time without prejudice to my future medical care. I further understand that while the results of this study may be published, my personal identity will not be disclosed without my separate consent, unless as required by law. Martin J. Cline, M.D., the Principal Investigator (Room 37-068, UCLA Center for the Health Sciences, Los Angeles, California 90024, phone number 213-825-7865), and/or his designated physician associates have offered to answer any further questions I might have at any time.

I understand that if I have any questions, comments, or concerns about the study or the informed consent process, I may address them to the Associate Vice Chancellor-Research, Room 3134, Murphy Hall, UCLA Los Angeles, CA 90024 (213-825-8714). On signing this consent form, I acknowledge receiving a copy of the form, as well as a copy of the "Subject's Bill of Rights." I understand that the University of California will provide any and all medical treatment reasonably necessary for any injury or illness that I suffer as a direct result of my participation in this research project, except when the injury or illness is a consequence of the medical research procedure that is designed to benefit me directly.

PATIENT	PHYSICIAN
DATE	WITNESS

Patient is a Minor or unable to sign because of ______________

____

PARENT OR LEGAL GUARDIAN	DATE

MJC:gd

HSPC #79-05-468

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RIGHTS OF HUMAN SUBJECTS
IN
MEDICAL EXPERIMENTS

Any person who is requested to consent to participate as a subject in a research study involving a medical experiment or who is requested to consent on behalf of another has the right to:

1. Be informed of the nature and purpose of the experiment.
2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized.
3. Be given a description of any attendant discomforts and risks reasonably to be expected from the experiment.
4. Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.
5. Be given a disclosure of any appropriate alternative procedures, drugs or devices that might be advantageous to the subject, and their relative risks and benefits.
6. Be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise.
7. Be given an opportunity to ask any questions concerning the experiment or the procedure involved.
8. Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation in the medical experiment without prejudice.
9. Be given a copy of any signed and dated written consent form used in relation to the experiment.
10. Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.

1/79

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DEPARTMENT OF MEDICINE
UCLA SCHOOL OF MEDICINE
CENTER FOR THE HEALTH SCIENCES
LOS ANGELES, CALIFORNIA 90024

March 8, 1983

Mr. Steven Owens
Subcommittee on Investigations
and Oversight
House Annex No. 1, Room 822
Washington, DC 20515

Dear Mr. Owens:

I have enclosed a copy of the consent signed by my Italian patient's parents. As you can see, the hospital there had nothing so official as the consent we formulated here for the UCLA Human Subject Protection Committee. The notice of consent signed by my Israeli patient remains in Israel.

Sincerely,

Martin Cline

Martin J. Cline, M.D.
The Bowyer Professor of
Medical Oncology

MJC:gd

Encl.

In data 8/7/1980 presso il Centro per la Microcitemia della Clinica Pediatrica II, dove sono seguiti i nostri figli Maria Addolorata e Andrea, affetti da morbo di Cooley,(β-talassemia omozigote), ci è stato proposto dal Prof. Nicola e dalla dott.sa Gabutti di sottoporre Maria Addolorata ad un nuovo trattamento terapeutico, che dovrà essere effettuato a Napoli presso l'Istituto di Patologia Medica dell'Università (Prof. Condorelli) in collaborazione con l'university ofCalifornia di Los Angeles(Prof. Cline).
Il procedimento consiste nel prelievo di cellule di midollo osseo, nella loro induzione a sintetizzare emoglobina attraverso l'immissione in esse del gene per le catene emoglobiniche e del gene per la timidinchinasi e nella loro reintroduzione per via endovenosa. Il trattamento è preceduto dall'irradiazione con 200 r di una piccola superficie di una tibia.
I principi, lo scopo, la metodologia e i rischi eventuali del procedimento ci sono stati illustrati in modo esauriente e comprensibile. Siamo stati avvertiti che tale terapia è stata sperimentata con successo sugli animali ma mai sull'uomo.
Coscienti dell'importanza che riveste questo nuovo metodo per la cura dei nostri figli e per tutti i talassemici, sentito il parere favorevole coscientemente e liberamente espresso da Maria Addolorata, accettiamo di nostra volontà, senza coercizioni, di sottoporre nostra figlia al trattamento.

Maiorano Luigia

Congressional Research Service
The Library of Congress

Washington, D.C. 20540

Translation (Italian)

At the Center of Mircrothemia of the Pediatric Clinic II where our children Maria Addolorata and Andrea, suffering from Cooley's disease, (Homozygotic Thalassemia) were treated, Prof. Nicola and Dr. Gabutti on July 8, 1980 suggested to us that Maria Addolorata should undergo a new therapeutic treatment at the University's Institute of Medical Pathology (Prof. Condorelli) in Naples in cooperation with the University of California in Los Angeles (Prof. Cline).

The procedure calls for the sampling of cells from the bone marrow, their induction for the purpose of synthesizing hemoglobin through the immission of genes by way of the hemoglobinic chain and genes through the "timidichinasi" /term unknown/ and their reintroduction through the intravenous system. The treatment will be preceded by a 200 r radiation of a small surface of the tibia.

The principles, the purpose, the methodology and the possible risks involved in this procedure have been exhaustively and comprehensibly explained. We have been informed that a therapy of this sort has successfully been carried out on animals but never on man.

Fully aware of the importance this new method may have for the treatment of our children and of all others suffering from thalassemia and having heard Maria Addolorata's favorable consciously and freely expressed opinion we agree of our own will and without any duress that our daughter undergo the treatment.

two signatures /illegible/

Translated by Paul Vidal
CRS - Language Services
4/5/83 - amc

Mr. GORE. I would like to thank you very much for your willingness to come. I know it's a problem, it would be for me, be a matter of some difficulty, I think that it's extremely helpful as we try to develop a better understanding where we are apt to be going here to have your views and your input and I deeply appreciate your willingness to come and testify.

Dr. CLINE. Thank you.

Mr. GORE. Thank you.

Our next witnesses are on a panel. Dr. Bernard Davis, professor of bacterial physiology at Harvard University Medical School in Boston; Dr. Liebe Cavalieri, professor of biochemistry, Cornell Medical College, Prof. Troy Duster, director, Institute for the Study of Social Change, University of California; and Dr. Elna Nightingale, senior scholar-in-residence, Institute of Medicine, National Academy of Sciences.

I would like to welcome all four of you to the subcommittee's hearings. We appreciate your presence and without objection the full text of your prepared statements will be included in full in the record.

Again, let me remind you that some witnesses on our second panel are under time constraints, so if there are portions of your prepared statements that you feel that you might be able to summarize without doing them injustice, then I invite you to do that.

We would like to begin with you, Dr. Davis. Welcome. I appreciate the fact that you have been watching these proceedings and appreciate your appearance here today, so go ahead.

STATEMENTS OF DR. BERNARD DAVIS, PROFESSOR OF BACTERIAL PHYSIOLOGY, HARVARD UNIVERSITY MEDICAL SCHOOL, BOSTON, MASS.; PROF. TROY DUSTER, DIRECTOR, INSTITUTE FOR THE STUDY OF SOCIAL CHANGE, UNIVERSITY OF CALIFORNIA, BERKELEY, CALIF.; DR. ELENA NIGHTINGALE, SENIOR SCHOLAR-IN-RESIDENCE, INSTITUTE OF MEDICINE, NATIONAL ACADEMY OF SCIENCES, WASHINGTON, D.C.; AND DR. LIEBE CAVALIERI, PROFESSOR OF BIOCHEMISTRY, CORNELL MEDICAL COLLEGE, MEMBER, SLOAN-KETTERING INSTITUTE, RYE, N.Y.

Dr. DAVIS. Thank you very much. It is a privilege to be able to testify here. Having had a chance to watch the proceedings, I find that much of what I defend in my statement doesn't seem to need any more defense, so I will eliminate much of this material and will expand my comments on some of the areas of controversy that have come up.

Two years ago a letter from three major religious groups led to the study of the problems of genetic engineering by a Presidential commission, and this letter noted that the very term genetic engineering suggests the danger. Indeed, I think it's a very unfortunate term to apply to an activity that includes gene therapy. It also includes nonmedical applications of the same techniques.

The therapeutic part, of course, is strictly within the humanitarian tradition of medicine, and I would stress the importance of distinguishing sharply between the medical uses of these techniques and the nonmedical uses, which would aim at manipulating other aspects of human beings than those concerned with prevention or cure of disease. There have been many scenarios of these nonmedical uses, such as the mad scientist creating a monster, or various modifications in physical or mental attributes. But it is my impression that what most people fear, when they worry about where we are going with this new power, is the eventual control of behavior for eugenic or political purposes.

The report of the Commission presents a thoughtful and responsible analysis of the issues, and it comes out most reassuringly in favor of proceeding with research on gene therapy per se, I will therefore not proceed to defend that any further, and I would like to express my gratification that all of the witnesses, including the representatives of the originally concerned religious groups seemed to be quite convinced that gene therapy itself is not a problem.

The major issue set up before the Presidential commission has thus apparently been solved in a most responsible and salutory way. Nevertheless, there are no doubt residual public concerns that we will all have to face and I would go a little into the history of why we have to face them.

I think most of the discussion of where we are going with these new powers has proceeded on the assumption that two developments are insolubly linked: if we develop the possibility of correcting the genetic cause of any disease, we would also be creating the possibility of a brave new world with governments using the same techniques for deliberate interference with human nature. This assumption became widely accepted when news of a spectacular scientific advance a dozen years ago, the isolation of a gene by Jonathan Beckwith and his colleagues, was accompanied by an even more newsworthy announcement: He regretted this success, because he believed that this line of research would soon lead to the power to manipulate human genes, and he did not trust our political system to insure that this power would be used only to benefit the people.

Quite apart from any preference for one or another political system, if I believed that we would indeed be reaching the capacity to use techniques of genetic modification to program human behavior in any general way I would also feel uneasy at that prospect, in the hands of any political system. But on purely technical grounds I disagree with the judgment that that power is in sight, or even is likely as far ahead as we can look. My reasons are the following.

First, the therapy even of single-gene defects is not yet around the corner, though replacement of defective cells is beginning to look feasible for those cells that function in widely distributed, loosely organized locations. These include the precursor cells in the bone marrow that give rise to the red cells and the white cells of the blood, and the precursor cells that give rise to our specific immune responses. There are still many technical obstacles to overcome, but I agree that therapy is in sight.

When cells are arranged in a highly specialized way, as in the liver or the kidney, the prospect of replacing them, or of introducing a desired gene into them in a reliably controlled way, is much dimmer. And when we consider the technical problem of modifying behavior genetically we are dealing with an infinitely more complex pattern of cellular organization, involving a network of about

10 trillion specific connections between about 10 billion cells in the human brain. An enormous number of genes must be involved in the development of this circuitry, and any particular trait, such as intelligence or aggressiveness, must be influenced by a large number of these genes, interacting with each other and with the environment. It is therefore not surprising that we cannot yet identify a single specific behavioral gene, while we can identify several hundred that cause hereditary diseases.

To achieve a specific modification of behavior, involving altered circuitry,we would have to identify a set of genes that each have a small effect on a trait, isolate these genes, and transfer them together. Both the identification and the transfer would be very much more difficult than what we face with single-gene defects.

Of course, behavior is also affected not only by circuitry but also by the surroundings of our brain cells, particularly hormones, and we know that aggressiveness can be influenced by the level of sex hormones and adrenal hormones. And the only prospect I can take seriously in the area of genetic modifications of behavior in the foreseeable future would be modification of the level of such hormones, which exert only vague and nonspecific effect on behavior, rather than specific pinpointed ones. In that situation it would probably be easier to control the level of the hormone directly rather than by changing genes.

Another important difference is that behavior depends heavily on environmental influences as well as on genes. Accordingly, the effect of genetic changes on behavior would not be as sharply predictable as the effect of replacing a defective protein in a blood cell. An even greater obstacle arises from the difference in the time at which different genes act: most of the genes that contribute to individual differences in behavior must do so by guiding development of the intricate circuitry of the brain, and so they will have done their work before birth. And gene transfer could not conceivably rewire an already developed brain.

Finally, if some limited degree of genetic manipulation of behavior should ever become feasible, we must recognize that it would require cooperation of the subjects; and any population willing to cooperate in this way would already have lost its freedom. Moreover, this means of manipulating personalities would have to compete with other, less elaborate and less costly means, some already at hand. These include the familiar psychological methods, as well as possibilities provided by pharmacology, neurosurgery, and even eugenics.

I would conclude that behavior modification in already existing people through genetic changes is not impossible, but it is very limited in what it could accomplish, and it is still distant.

Let me now consider the possibilities for germ line or embryonic modifications. This procedure could overcome what I would consider the strongest of the obstacles to behavior control by genes, namely, the fact that we cannot rewire the brain. If we could get the genes into the embryo we could influence the circuitry of its brain.

In the last 2 days there has been a good deal of discussion of the general problem of modifying embryos. Dr. Fletcher emphasized that this extension of gene therapy creates a special moral problem, because it would influence future generations. I am not convinced, if what you are doing is simply curing a clearly undesirable gene.

After all, the effect on future generations would be exactly the same if one used prenatal diagnosis and abortion to eliminate a defective fetus and then allowed a healthy fetus in the same family to survive. However, I do see another kind of serious moral problem inherent in embryonic or germ line gene replacement: That is the responsibility for undertaking this step if the techniques have any uncertainty about them at all—and I am afraid they are bound to have uncertainty.

Let me further contrast the two approaches. To replace defective bone marrow cells, you might take a set of cells from the patient and expose them in one way or another to DNA carrying the gene you want to get in. A small fraction of the cells would pick up that DNA, and you can select for that fraction. You then cultivate these cells, get a cell line that seems to be genetically stable, and now put a large number of those cells back into the patient. If enough of these repopulate the depleted bone marrow you achieve your objective. At each of these stages you are dealing with a great many cells, and they need not all work. Moreover, if it turned out that the implantation of the gene was not as stable as you hoped for, you could repeat the procedure later and have a second wave of replacement by good cells.

With the embryo, in contrast, inserting a desired gene might create a defect in the gene in which the insertion takes place, or it might create an imbalance in the genes by having multiple copies of what you are inserting. You could thus introduce harm along with the benfit. It's going to be very difficult to be really certain that we can manipulate a germ cell and cause no change other than the one that we wish for.

I see that as very, very far off. And if we had experiments in mice that gave us something as fantastic as a 99-percent success rate in producing a desired change in a germ line cell, would we wish to modify unborn persons in this way, if one percent were going to be more defective? The answer is evident.

My general conclusion, then, would be that the technical possibility of introducing ghenes into cells is already here, but its reliable use is very distant. It is important for this kind of research to proceed in animals for the sake of advancing developmental biology, but not to proceed toward early application in human beings.

Let us now look at the problems of inserting genes into human germ line cells in order to modify behavior. This procedure would get around a limitation that I have discussed in connection with modifying people already born: The inability of introduced genes to rewire an already formed brain. In an embryo inserted genes could influence that wiring.

The most important limitation here, I believe, is yet another one, which has not been prominent in discussions of various scary scenarios: motivation. Every embryo or fertilized egg contains a novel, unknown set of genes, and I find it hard to see why anyone would wish to go to great trouble to insert known behavioral genes into such an unknown background. If a couple wished to have a smarter or stronger child than their own genes deemed likely to provide they might conceivably be interested in using such genetic manipulation—but the result could still not be predicted accurately, because of the unknown genes in the embryo. It would be much simpler to get gene cells from other individuals with the desired properties. This kind of molecular manipulation of embryos therefore seems to me extremely unlikely to be tempting, quite apart from its technical difficulties, for the foreseeable future.

Let me now return to gene therapy. All the witnesses that I have heard seem to be in agreement that research on gene therapy does not present a moral problem, but we still may face moral problems in the experimental introduction of these techniques in human beings. I would suggest that the problems are essentially the same as those faced by any new therapy, whether medical or surgical. There is always a tension between the desire to make a new mode of therapy available as soon as possible and the need to have its safety and efficacy thoroughly tested first in animals.

In resolving these problems the medical profession relies on a long tradition, now supplemented by the existence of bioethics review boards. I do not see any compelling reason for special legislative treatment for gene therapy. I would think it could be taken care of by the kinds of boards that have already acted in the case we have just discussed that of Dr. Martin Cline and that would act in future cases. However, because this approach is so novel and has been so much in the public eye it should be handled by the profession with great care.

Let me close by emphasizing the need to protect the search for basic knowledge from being restricted by those who fear possible undesirable applications. All knowledge is double-edged; and we simply cannot foresee all the applications, and all the social consequences, of any discovery. We can serve society best not by blocking any particular knowledge but by better controlling its applications. In the physical sciences we have begun to resist certain applications that are too dangerous to people or damaging to the environment. If such applications appear in biology they should also be prohibited. But in the application of molecular genetics to man, where enormously beneficial results are in sight, I do not yet see any threats in the near future from which society needs protection.

Now, I would like to take a minute or two to offer thoughts on the question of what might be accomplished by a special commission, but since time is more pressing and you have been asking the witnesses that question regularly, would you prefer I complete this, or——

Mr. Gore. If you can summarize it, it would be helpful.

Dr. Davis. Thank you. The question is, should there be a permanent commission and, if so, what kind. So far all the witnesses have agreed that there should be. I would like to express some doubt about the value of such at commission a this time.

For monogenic therapy, I believe we have all agreed that there are no inherent moral problems; there are only problems of specific precautions and timing, as in all therapy. It is difficult for me to see the need for a special commission to build up a new body of ethics around this aspect of the problem. I think our existing body of ethics governing the introduction of experimental new therapy is sufficient. We would create unnecessary problems if we had a body in Washington whose permission was required before one could go ahead with experimentation in this field.

The idea of such a commission may seem like a logical parallel to the Recombinant DNA Advisory Committee [RAC] of the NIH, which was set up to provide the rules governing experimentation with possibly hazardous recombinant bacteria. In that case we were dealing with fear of a public health problem, from products that might get out of hand and not be readily reversed. Even though that perception did not prove to be accurate, it was a widely held perception, and so the creation of a central regulatory body was justified and necessary. However, with genetic engineering in man we are not dealing with any potential emergency, in the form of an epidemic; we are dealing with the ethical issues that would arise if it became possible to apply genetic engineering to humans for such nonmedical purposes as behavior modification or cloning.

I agree that if such nonmedical applications start to come into sight as real technical possibilities, strict control by society, and even complete prohibition for some procedures, would be required. But I do not believe any of these threats to our welfare are close enough to convince me of the need for a commission set up specifically to survey future ethical problems of genetic engineering. If such problems do not arise for years the commission would have little to do; and if and when they do arise, they would follow on animal experiments that would give us ample warning of the need for regulation.

If we set up a committee that does not have much of a job to do it not only would be wasteful of resources, but there is some danger it might even try to find things to do and hence begin to interfere with desirable activities. Accordingly, I would like to see the surveillance of moral problems in this area absorbed into a broader framework—that of a continuing commission concerned with the whole field of biomedical ethics, not singling out genetic engineering.

[The prepared statement of Dr. Davis follows:]

STATEMENT OF BERNARD D. DAVIS

INHERENT LIMITATIONS OF GENETIC ENGINEERING IN MAN

The term "genetic engineering" is an unfortunate one, when applied to human beings. It carries overtones of a cold attitude toward people, as objects to be manipulated and remolded. Yet the goal of those working toward human applications of this technique is gene therapy—the replacement of the single defective genes that cause various hereditary diseases; and this aim is strictly within the humanitarian traditions of medicine. It is therefore essential, in discussing future prospects, to distinguish sharply between gene therapy and non-medical uses of genetic manipulation. The non-medical use that most people fear, of course, is the control of behavior for eugenic or political purposes.

Therapeutic and non-therapeutic applications not only differ in their aims: they also differ strikingly in the likelihood that we will have to deal with them in the foreseeable future, because they face very different technical problems. Unfortunately, however, most of the discussion of the subject has proceeded on the assumption that the two developments are indissolubly linked: if we developed the possibility of correcting the genetic cause of any disease we would also be creating the possibility of a Brave New World, with governments using the same techniques for deliberate interference with human nature.

This assumption became widely accepted when news of a spectacular scientific advance a dozen years ago, the isolation of a gene by Jonathan Beckwith and his colleagues, was accompanied by an even more newsworthy announcement: he regretted this succuess, because he believed that this line of research would soon lead to the power to manipulate human genes, and he did not trust our political system to ensure that this power would be used only to benefit the people. Quite apart from any preference for one or another political system, if I believed that we would indeed be reaching the capacity to use techniques of genetic modification to program human behavior in any general way I would also feel uneasy at that prospect, in the hands of any political system. But on purely technical grounds I disagree with the judgment that that power is in sight, or even is likely as far ahead as we can look. My reasons are the following.

First, the therapy even of single-gene defects is not yet around the corner, though replacement of defective cells is beginning to look feasible for those cells that function in widely distributed, loosely organized locations. These include the precursor cells in the bone marrow that give rise to the red cells and the white cells of the blood, and the precursor cells that give rise to our specific immune responses. But even here there are still many technical obstacles to overcome.

When cells are arranged in a highly organized way, as in the liver or the kidney, the prospect of replacing them, or of introducing a desired gene into them in a reliably controlled way, is much dimmer.

When we consider the technical problem of modifying behavior genetically we are dealing with an infinitely more complex pattern of cellular organization, involving a network of about 10 trillion specific connections between about 10 billion cells in the human brain. An enormous number of genes must be involved in the development of this circuitry, and any particular trait, such as intelligence or aggressiveness, must be influenced by a large number of these genes, interacting with each other and with the environment. It is therefore not surprising that we cannot yet identify a single specific behavioral gene, while we can identify several hundred that cause hereditary diseases.

Accordingly, the only prospect I can take seriously in this area, for the foreseeable future, would be a limited, vague alteration of behavior by influencing the level of various hormones. To achieve any more specific modification of behavior, involving altered circuitry, we would have to identify a set of genes that each have a small effect on a trait, isolate these genes, and transfer them together. Both the identification and the transfer would be very much more difficult than what we face with single-gene defects.

Another important difference is that behavior depends heavily on evironmental influences as well as on genes. Accordingly, the effect of genetic changes on behavior would not be as sharply predictable as the effect of replacing an enzyme in a blood cell. An even greater obstacle arises from the difference in the time at which different genes act: most of the genes that contribute to individual differences in behavior must do so by guiding development of the intricate circuitry of the brain, and so they will have done their work before birth. And gene transfer could not conceivably rewire an already developed brain. In principle, one could circumvent this difficulty by replacing genes in germ cells. But this procedure would be useless, for one would be investing great effort to change some genes in a germ cell whose other genes were still an unknown, chance combination.

Finally, if some limited degree of genetic manipulation of behavior should ever become feasible, we must recognize that it would require cooperation of the subjects; and any population willing to cooperate in this way would already have lost its freedom. Moreover, this means of manipulating personalities would have to compete with other, less elaborate and less costly means, some already at hand. These include the familiar psychological methods, as well as possibilities provided by pharmacology, neurosurgery, and even eugenics (that is, selective breeding for the desired traits).

I cannot escape the conclusion that the rumors of the dangers of genetic blueprinting of behavior have been enormously exaggerated, and they have aroused much more public apprehension than the facts warrant. At the same time, it is clear that the development of effective gene therapy, even for a limited number of hereditary diseases, would be one of the greatest triumphs of medical science. And even if the procedure should prove to be expensive, its benefits would convert a miserable, helpless, and often brief life into a healthy one, and the costs would be amortized over that lifetime. This kind of research therefore deserves support and approval, rather than apprehension. It would be a tragedy if moral objections, based on fear of misuse of the same techniques, should interfere with such support and approval.

The fear of misuse that I have just discussed is rational, though based on an incacurate perception of the facts. But some may also object to this research on the basis of a more abstract and less rational principle: that it is immoral of dangerous to "play God" and tamper with a person's genes, since these define his essential individuality. I find it difficult to take this objection seriously. It brings to mind a curious response when chemotherapy against syphilis was introduced by Paul Ehrlich early in this century: some objected on the grounds that the disease was God's natural punishment for illicit sexual behavior. That vindictive view did not prevail, and I am confident that any parallel view of hereditary defects, as inevitable acts of God, will not prevail either. On the contrary, as our power to identify and to correct defects increases our notion of rights will inevitably move to include the right to start life without a severe handicap, if it might be prevented.

If we agree, then, that gene therapy by itself does not present a moral problem, we still face the question of possible moral obstacles to the experimental introduction of these techniques in human beings. I would suggest that this problem is essentially the same as that faced by any new therapy, whether medical or surgical. There is always a tension between the desire to make a new mode of therapy available as soon as possible and the need to have its safety and efficacy thoroughly tested first in animals. In resolving these problems the medical profession relies on a long tradition, now supplemented by the existence of bioethics review boards. I do not see any compelling reasons for special legislative treatment for gene therapy. However, because this approach is so novel and has been so much in the public eye it should be handled by the profession with great care.

I would now like to consider another type of genetic manipulation of humans that has seemed much closer than gene replacement: cloning. This creation of genetic copies of an individual has been successfully accomplished with frog embryos, by implanting nuclei from their body cells into egg cells. Ten years ago it seemed self-evident that improvements in technique would sooner or later extend the procedure to mammals, and also to the copying of tested adults rather than of undefined embryos. This scientific advance, if possible, would be of obvious value in agriculture, in the copying of prize animals.

The extension of cloning to man would raise such serious moral problems that I would oppose it. However, it now seems doubtful that we will have to face the problem. For while we know that all the different kinds of cells in our bodies contain essentially the same set of genes, recent work strongly suggests that as embryonic cells give rise to fully differentiated cells some of their genes change. Adult cells may therefore never be able to initiate clones. If this proves to be true the cloning of mammalian adults may well be unachievable, for fundamental reasons rather than for reasons that might be overcome by advances in technique. Human cloning by nuclear transplant, aimed at copying individuals with already demonstrated traits, would then lose its potential interest—and its threat.

Embryos, on the other hand, encounter no such problem as a source of clones. In fact, such cloning has already been accomplished in mice, not by nuclear transplantation but by separating the cells of a very early embryo and using each to start a new embryo. But while this procedure is indeed cloning, in the technical definition of the term, it is cloning of an unknown new individual rather than copying of a known. It is thus not a violation of our natural process of reproduction, which makes each individual unique by randomly recombining genes from the two parents; it is simply amplification of the process of producing identical twins. The motivation for this form of cloning is not nearly as obvious as that for cloning adults. I therefore do not see a problem that merits legislative attention now, though one might conceivably arise in the future.

Finally, we should note that molecular genetics has already made concrete contributions to medicine in a third, rapidly expanding area: prenatal diagnosis of hereditary defects. This development is of great benefit to those parents who both carry a recessive defect in the same gene: instead of accepting the 25% risk of a defective offspring, or also denying themselves children, for several diseases they now have the choice of solving the problem by prevention, even though it cannot yet be solved by gene therapy.

Let me close by emphasizing the need to protect the search for basic knowledge from being restricted by those who fear possible undesirable applications. All knowledge is double-edged; and we simply cannot foresee all the applications, and all the social consequences, of any discovery. We can serve society best not by blocking any particular knowledge but by better controlling its applications. In the physial sciences we have began to resist certain applications that are too dangerous to people or damaging to the environment. If such applications appear in biology they should also be prohibited. But in the application of molecular genetics to man, where enormously beneficial results are appearing, I do not yet see any threats from which society needs protection.

Mr. GORE. Thank you.

We will hold questions until the panel is over with.

I would like to call now on Dr. Liebe Cavalieri, professor of biochemistry, Cornell Medical College and member of the Sloan-Kettering Institute.

Dr. CAVALIERI. Thank you.

The major question facing the scientific community today involves priorities: What are the important questions? Which problems are to be solved first? In earlier times, funds and resources were virtually in excess and these questions did not surface; but, more importantly, the nature of scientific discovery has undergone a qualitative change in recent decades. Science and science-based technology now affect every aspect of global society, from the engineering of nuclear weapons to human genetic engineering. For better or worse, these are major human activities; but scientists have not developed a commensurate social conscience, that takes into consideration the profound societal consequences of what they may find in the laboratory. In the habitual manner of our times, scientists are pursuing their interests and then rationalizing the pursuit by looking for uses for their discoveries, whether society needs them or not, rather than starting with the most pressing problems and looking for solutions. This may have been acceptable in the past, but I am not sure society can afford this luxury right now, when it is facing an alarming series of threats that have recently become apparent: The energy problem, the "greenhouse effect," acid rain, ozone depletion, water and air pollution by industrial products and waste, accelerating soil erosion and desertification, species extinction, exhaustion of renewable resources such as water and forests faster than they can be replenished, impending depletion of mineral resources, population growth, and the devotion of a large part of our resources to the arms race.

In spite of all these problems, Federal funding, which supports a large part of the research and development in the United States, is not guided by an overall plan that identifies the major problems we face in our country and encourage research in those areas. The rush toward genetic engineering is the latest case in point.

We have witnessed in the 20th century two of the most profound scientific discoveries of all times: Nuclear fission that gave us the bomb, and DNA, the genetic substance, that is now giving rise to genetic engineering. These discoveries confer on humans a power for which they are morally and psychologically unprepared. The history and the development of these technologies are disturbingly similar in many ways, for they deal with manipulations and disruptions of the basic material of the physical universe.

Both are pervasive, with the potential to affect adversely the entire planet; and both violate the integrity and continuity of life—some even think its sacredness, as the President's Commission brought out.

While we contemplate nuclear war in the name of security, or a more sustained attack on nature through genetic engineering in the name of progress, we ought to be wondering about the necessity and wisdom of these ventures.

Fifty years ago, physicists were studying the fundamental properties of the atomic nucleus when they discovered atomic fission.

There was no question about it, this finding defined the bomb. The discovery led immediately to the application.

Some physicists were cautious; others not. Rutherford said in 1933:

> A lot of nonsense has been talked about transmutation. Our interest in the matter is purely scientific, and the experiments which are being carried out will help us to a better understanding of the structure of matter. These transformations of the atom are of extraordinary interest to scientists, but we cannot control atomic energy to an extent which would be of any value commercially, and I believe we are not likely to be able to do so.

But nuclear science went forward into the commercial and military applications which are now a heavy social burden.

Similarly, the discovery of the enzymes that specifically cleave DNA defined genetic engineering, and little time elapsed between discovery and application. Does recombinant DNA technology represent good science? Yes. You have heard in previous testimony about its usefulness in investigations of embryonic development and gene structure. Are applications of genetic engineering apt to be useful? Some are. There may be a rare drug or protein that will help to cure some diseases. But I am concerned about the fact that there are about 150—I recently heard 300—genetic engineering firms which are producing or are about to produce an entire array of products whose main feature is their marketability rather than their potential for improving the human condition.

Genetic engineers have many visions. They plan to introduce foreign genes into crop plants in the hope of solving the problem of world hunger. But food experts and agronomists recognize that enough is already produced to feed everyone in the world. Distribution is the problem; it is not scientific, but rather economic and political.

The world population is now about 4.3 billion. It is expected to increase to about 8 billion after the turn of the century, thence to about 16 billion in 2040. Although we have the theoretical capacity to feed all the 4.3 billion people alive today, nevertheless, in the underdeveloped countries 1 billion people receive too few calories.

One of the fundamental limits to food production is the amount of available arable land, which is estimated at approximately 8 billion acres. Each person requires about 1 acre—including space for food production, roads, industry, living space, and disposal of pollutants—in order to live at a civilized level. The maximum limit on world population size is thus automatically set at approximately 8 billion. For that, we are going to get into deep trouble. In the United States, we are already close to the theoretical limit of what an acre of land can be made to produce. Throughout the world, factors such as water supply impose a natural limit. In addition, agriculture is in ecological competition for natural resources used for other purposes: Water is needed for powerplants, factories, mines, and other types of production; land is continuously taken for highway and other nonagricultural uses.

It is obvious that it would be naive to attempt to solve the food problem with recombinant DNA technology. Even if that technology should someday succeed in producing plants that can fix atmospheric nitrogen, the most that could be hoped for would be a small contribution to a temporary respite—a technological fix that has no bearing on the fundamental population problem and might have adverse side effects that would exacerbate the situation by producing ecological instability.

Bacteria that will consume oil from oil spills on the oceans have been produced. In addition to ecological questions, the social implications of this procedure are far-reaching. It has been shown that crude oil spilled from faulty tankers has an adverse effect on marine life. The application of vast numbers of bacteria to consume the spill would doubtlessly lead to mutant forms with an altered metabolism, so that some might find a niche in the oceans or even on land, causing ecological disturbances. Moreover, the oceans—which lie in the public domain—would be left to the manipulation of three private groups—tanker and oil companies and the producer of oil-eating microorganisms. This situation, as well as others in which there is an intentional release of genetically engineered organisms or other pollutants into the public environment, present difficult questions for which there are no simple institutional answers. But it is time the questions were faced. The commercial wheels of genetic engineering have already been set in motion with total disregard for the commons. A similar nonsolution has plagued us for 30-odd years since nuclear power was born; there is still no satisfying answer to the question of the disposal of their radioactive waste.

Another vision of genetic engineers involves gene therapy. Molecular biologists hope to be able to perform single-gene replacement therapy in cases where a single gene results in a genetic disease such as sickle-cell anemia. As far back as 1977, a protocol for this type of therapy was discussed publicly. A scientist described an experimental protocol in which the desired genes could be introduced into bone marrow cells outside the body; these cells can then be reintroduced into the body of an afflicted individual. But the goal of this type of single gene replacement therapy has already been superseded by one in which a single gene is replaced in the germ line as well as in the somatic cell. The aim is to correct the gene in future progeny. As a scientist commented during the review of the draft report of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research:

> We're not that concerned about doing gene therapy for an individual person. It's to correct that gene from then on. By the time we're probably successful doing gene therapy at all, one of the aspects of that will be to be able to direct that gene into the cell type you want. * * * And one can then affect, at least in the male, the germ line at the same time you are affecting the liver of whatever.

Perusal of the draft report and the proceedings of the review shows that the commissioners and the consultants did a great deal of work, but the draft report is disappointing in a number of instances. The question of species barriers is treated in a rather condescending manner; the wisdom of evolution is questioned as though one should expect predictive value from it; there was much waffling in the proceedings around the question of whether the line should be drawn in human genetic engineering. The very consideration of a line implies that genetic engineering should proceed. Perhaps the final report will mark an improvement. In the discussion of the improvement of the human design, a fundamental sociophilosophical question was mentioned only in passing: how can we know what attributes will be desirable for future humans, who in all likelihood will have a different set of standards and mores from the present creators of the new design?

It was implied in the report as well as in the proceedings of the review that human genetic engineering would go forward; therefore, the questions discussed had more to do with how it should proceed rather than whether it should proceed. The following paragraph taken from the draft report illustrates this point:

> One question that traditional experiments will have difficulty answering is whether something important may be lost as disease genes are eliminated. On one level this is a long-term question about human evolutionary changes that might follow upon widespread alteration of the human gene pool, which will probably not even be a theoretical problem for centuries. Gene therapy is likely to be uncommon even in the industrialized world for decades, gene surgery for considerably longer, and designed genes affecting the whole species more distant still.

It was taken for granted that genetic engineering should have the green light even if there are ethical and moral costs. When one of the commissioners was asked if he was opposed to intervening in the human germ line he answered "No"—but care should be exercised.

I am concerned about the tone and intent of the report, in relation to the attitudes of the public. The report and the proceedings of the meeting give the distinct impression that genetic engineering is desirable and that all will be well if we are cautious.

I do not feel that this is in accord with public opinion. In giving public lectures on this subject I have observed that the public is leary of genetic engineering and certainly does not feel any pressing need for it. Whose view of the public interest does the report represent? Should genetic engineering be forced on the public? In a democracy, should decisions involving the public environment and the very nature of man be left to a few special interests?

Finally, I would remind you that animal experiments altering the germ line through manipulation of the embryo in vitro with recombinant DNA have already been done. Dr. Edwards in England has been growing human embryos in vitro up to the 9-day stage. The technology for intervention in the human germ line is here.

Thank you.

[The prepared statement of Dr. Cavalieri follows:]

STATEMENT OF LIEBE F. CAVALIERI

The major question facing the scientific community today involves priorities: What are the important questions? Which problems are to be solved first? In earlier times, funds and resources were virtually in excess and these questions did not surface; but, more importantly, the nature of scientific discovery has undergone a qualitative change in recent decades. Science and science-based technology now affect every aspect of global society, from the engineering of nuclear weapons to human genetic engineering. For better or worse, these are major human activities; but scientists have not developed a commensurate social conscience, that takes into consideration the profound societal consequences of what they may find in the laboratory. In the habitual manner of our times, scientists are pursuing their interests and then rationalizing the pursuit by looking for uses for their discoveries, whether society needs them or not, rather than starting with the most pressing problems and looking for solutions. This may have been acceptable in the past but I'm not sure society can afford this luxury right now, when it is facing an alarming series of threats that have recently become apparent: the energy problem, the "greenhouse effect", acid rain, ozone depletion, water and air pollution by industrial products and waste, accelerating soil erosion and desertification, species extinction, exhaustion of renewable resources such as water and forests faster than they can be replenished, impending depletion of mineral resources, population growth, and the devotion of a large part of our resources to the arms race. In spite of all these problems, Federal funding, which supports a large part of the research and development in the United States, is not guided by an over-all plan that identifies the major problems we face in our country and encourages research in those areas. The rush toward genetic engineering is the latest case in point.

We have witnessed in the 20th century two of the most profound scientific discoveries of all times: nuclear fission that gave us the bomb, and DNA, the genetic substance, that is now giving rise to genetic engineering. These discoveries confer on humans a power for which they are morally and psychologically unprepared. This history and the development of these technologies are disturbingly similar in many ways; for they deal with manipulations and disruptions of the basic material of the physical universe. Both are pervasive, with the potential to affect adversely the entire planet; and both violate the integrity and continuity of life, some even think its sacredness, as the President's Commission brought out. While we contemplate nuclear war in the name of security, or a more sustained attack on nature through genetic engineering in the name of progress, we ought to be wondering about the necessity and wisdom of these ventures.

Fifty years ago physicists were studying the fundamental properties of the atomic nucleus when they discovered atomic fission. There was no question about it, this finding defined the bomb. The discovery led immediately to the application. Some physicists were cautious, others not. Rutherford said in 1933: "A lot of nonsense has been talked about transmutation. Our interest in the manner is purely scientific, and the experiments which are being carried out will help us to a better understanding of the structure of matter. These transformations of the atom are of extraordinary interest to scientists, but we cannot control atomic energy to an extent which would be of any value commercially, and I believe we are not likely to be able to do so."

But nuclear science went forward into the commercial and military applications which are now a heavy social burden.

Similarly, the discovery of the enzymes that specifically cleave DNA defined genetic engineering, and little time elapsed between discovery and application. Does recombinant DNA technology represent good science? Yes. You have heard in previous testimony about its usefulness in investigations of enbryonic development and gene structure. Are applications of genetic engineering apt to be useful? Some are. There may be a rare drug or protein that will help to cure some diseases. But I am concerned about the fact that there are about 150 genetic engineering firms which are producing or are about to produce an entire array of products whose main feature is their marketability rather than their potential for improving the human condition.

Genetic engineers have many visions. They plan to introduce foreign genes into crop plants in the hope of solving the problem of world hunger. But food experts and agronomists recognize that enough is already produced to feed everyone in the world. Distribution is the problem; it is not scientific but rather economic and political. The world population is now about 4.3 billion. It is expected to increase to about 8 billion after the turn of the century, thence to about 16 billion in 2040. Although we have the theoretical capacity to feed all the 4.3 billion people alive today, nevertheless, in the underdeveloped countries a billion people receive too few calories.

One of the fundamental limits to food production is the amount of available arable land, which is estimated at approximately 8 billion acres. Each person requires about one acre (including space for food production, roads, industry, living space, and disposal of pollutants) in order to live at a civilized level. The maximum limit on world population size is thus automatically set at approximately 8 billion. In the United States we are already close to the theoretical limit of what an acre of land can be made to produce. Throughout the world, factors such as water supply impose a natural limit. In addition, agriculture is in ecological competition for natural resources used for other purposes: water is needed for power plants, factories, mines, and other types of production; land is continously taken for highway and other nonagricultural uses.

It is obvious that it would be naive to attempt to solve the food problem with recombinant DNA technology. Even if that technology should someday succeed in producing plants that can fix atmospheric nitrogen, the most that could be hoped for would be a small contribution to a temporary respite—a technological fix that has no bearing on the fundamental population problem and might have adverse side effects that would exacerbate the situation by producing ecological instability.

Bacteria that will consume oil from oil spills on the oceans have been produced. In addition to ecological questions, the social implications of this procedure are far-reaching. It has been shown that crude oil spilled from faulty tankers has an adverse affect on marine life. The application of vast numbers of bacteria to consume the spill would doubtlessly lead to mutant forms with an altered metabolism, so that some might find a niche in the oceans or even on land, causing ecological disturbances. Moreover, the oceans—which lie in the public domain—would be left to the manipulation of three private groups—tanker and oil companies and the producer of oil-eating microorganisms. This situation, as well as others in which there is an intentional release of genetically engineered organisms or other pollutants into the public environment, present difficult questions for which there are no simple institutional answers. But it is time the questions were faced. The commercial wheels of genetic engineering have already been set in motion with total disregard for the commons. A similar non-solution has plagued us for thirty odd years since nuclear power was born; there is still no satisfying answer to the question of the disposal of their radioactive waste.

Another vision of genetic engineers involves gene therapy. Molecular biologists hope to be able to perform single-gene replacement therapy in cases where a single gene results in a genetic disease such as sickle cell anemia. As far back as 1977 a protocol for this type of therapy was discussed publicly. A scientist described an experimental protocol in which the desired genes could be introduced into bone marrow cells outside the body; these cells can then be re-introduced into the body of an afflicted individual.

But the goal of this type of single-gene-replacement therapy has already been superseded by one in which a single gene is replaced in the germ line as well as in the somatic cell. The aim is to correct the gene in future progeny. As a scientist commented during the review of the draft report [1] of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research: "We're not that concerned about doing gene therapy for an individual person. It's to correct that gene from then on. By the time we're probably successful doing gene therapy at all, one of the aspects of that will be to be able to direct that gene into the cell type you want . . . And one can then affect, at least in the male, the germ line at the same time you are affecting the liver of whatever".

Perusal of the draft report and the proceedings of the review shows that the commissioners and the consultants did a great deal of work, but the draft report is disappointing in a number of instances. The question of species barriers is treated in a rather condescending manner; the "wisdom" of evolution is questioned as though one should expect predictive value from it; there was much waffling in the proceedings around the question of where the line should be drawn in human genetic engineering. The very consideration of a line implies that genetic engineering should proceed. Perhaps the final report will mark an improvement. In the discussion of the improvement of the human design, a fundamental sociophilosophical question was mentioned only in passing: how can we know what attributes will be desirable for future humans, who in all likelihood will have a different set of standards and mores from the present "creators" of the new design?

It was implied in the Report as well as in the Proceedings of the review that human genetic engineering would go forward; therefore the questions discussed had more to do with how it should proceed rather than whether it should proceed. The following paragraph taken from the Draft Report illustrates this point. "One question that traditional experiments will have difficulty answering is whether something important may be lost as disease genes are eliminated. On one level this is a long-term question about human evolutionary changes that might follow upon widespread alteration of the human gene pool, which will probably not even be a theoretical problem for centuries. Gene therapy is likely to be uncommon even in the industrialized world for decades, gene surgery for considerably longer, and designed genes affecting the whole species more distant still". It was taken for granted that genetic engineering should have the green light even if there are ethical and moral costs. When one of the commissioners was asked if he was opposed to intervening in the human germ line he answered "No"—but care should be exercised.

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[1] Draft Report on the Social and Ethical Issues in Genetic Engineering with Human Beings, issued July 9, 1982.

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Mr. GORE. Thank you very much for a very thought-provoking statement. We will come back for questions after hearing our final two witnesses on this panel.

Next is Prof. Troy Duster, director, Institute for the Study of Social Change, University of California at Berkeley.

Mr. DUSTER. Thank you.

I would like to begin by acknowledging the complexity of the task of trying to sort and weigh the different levels of concern.

We have heard concern for individual human suffering, and for related issues that are ethical, biomedical, and theological.

My purpose is to direct attention to still another level, the hidden potential social implications of both gene screening and gene therapy.

Now, we know from birth control studies that having a technology and putting it into a population is not an automatic feature of the receiving population's uniform consumption. That is, we know from studies in various countries of the Third World that having the technology is not sufficient to having birth control. We know from studies of influenza vaccine that populations vary in their receptivity to that kind of new technology. We know from smallpox vaccination studies of the last 50 years that only when we coordinate certain kinds of policies of education and administration do we get a population receiving these vaccines successfully.

I want to argue that with gene therapy and gene screening, these social factors will play an even greater role in what happens with their consumption.

Before 1962, before we had gene screening, we all agreed upon certain health screening aspects in this country and the need for eliminating contagious diseases. We could agree that tuberculosis, venereal disease, and the plague, should be eliminated for public health reasons.

We could, therefore, get consensus about social planning. The reason, I think, is because these diseases cut across all lines, class, sex, race, and age. But the peculiar problem of gene screening and gene therapies is that they may overlap in a striking way with risk populations; with, for example, various racial groups and ethnic groups. Therefore, it is no longer possible to see the obvious public health issue in pursuing gene screening for everyone or gene therapies for everyone.

It could easily become a situation of bickering between my group, my disease—"I have the problem of sickle cell; you have the problem of thalassemia; you have the problem of Tay-Sachs," and groups could begin to disagree about which gene screening, or which gene therapy should get funding.

You have already seen that and it seems to me to be rather obvious. But, here, I think is something that may be hidden. There is a link I want to draw between gene screening and gene therapy. It is in the following question:

"Should we screen to prevent the birth of a child from genetic disorder, or should we develop a therapy to correct that disorder once the child is born?"

Depending upon a group's position in the society, that question might be answered quite differently. That is especially true if one group is doing the screening or the therapy in behalf of another.

Now, you can see the problem in relief against the old smallpox model.

A person could not surface with the right to have smallpox. We have the common interest of getting rid of this particular disease. But if I have the resources to develop a gene therapy for this particular kind of problem, and I am doing it in behalf of some group where I am not at risk, the issue of political and social power emerges quickly.

I want to repeat that this link is the key to my oral testimony and the key question for a policy recommendation.

The link with gene screening and gene therapy is in the question, should we allocate resources to screen to prevent the birth of an infant, or should we develop technologies for therapy to correct a disorder once the child is born?

Depending upon the position of a particular group in a society, their economic, or political power, or their social location, they will answer that question differently.

So, I would recommend there should be a policy of program planning by disease; that any general policy, any commission recommending policies, should permit flexibility, to permit disease-by-disease variation with a second recommendation, risk-populations with high representation in policy and program planning.

Does anyone think this is unwarranted?

We have on record the Tuskegee syphilis experiment funded by NIH for 40 years, and it's too fresh in our memory to dismiss the idea of a conflicting interest between biomedical researchers and the risk population.

My next point concerns the future trend of new technology in the next decade. It's easily conceivable that a new test will be available for pregnant women. The new DNA technology already permits us to bypass karyotyping for sickle-cell by amniocentesis. We may soon get a low-cost, low-risk relately benign test for many more women than those now using the test, those who are now consumers.

When that day arrives, members of different social groups will decide differently on what kind of child they will have. Whether one is from North European ancestry, Mediterranean, black, Jewish, or Asian, members from each group will answer that question quite differently based upon their respective social and cultural conceptions of normality.

In my written testimony I present data on different use patterns of California women. Upper middle-class whites use these centers most, for a variety of social and cultural reasons. That will be true, I want to argue, of gene therapy. We will not see this particular configuration of social life, but other configurations. People use them as individuals, of course, but those can best be understood, I think, by their social differences.

We know, for example, in California, that for some years women would fly over from Italy to receive thalassemia screening, while in the bay area, East Oakland, black women would refuse to receive the screening for sickle-cell anemia. The technologies available have little to do with the consumption pattern of population. Consumption patterns have to do with the receptivity of the population. In sum, the variable interests of different groups and their variable access to power means that there is something new with the new gene therapies and the new gene screening, something entirely new in health screening.

What I have found missing from the testimony so far is acknowledgment of the peculiar features of gene therapy and gene screening.

We have talked about what is coming, or about how these issues of the last 50 years are in a straight line. But there has been a general denial of the notion there we have here something unique.

I want to stress this uniqueness: that when gene screening begins to suddenly overlap socially visible risk populations, the question of who screens whom for what purpose is at the forefront of health planning.

There is no longer consensus.

As a policy recommendation, gene therapy research should have built into it social monitoring that looks at its implications. As for the format it takes, I have no recommendations. It could be the National Academy of Sciences; it could be the National Institutes of Health; it could have any number of forums which should be open to publication.

Let me close my remarks with an example.

You are aware of the X,Y,Y controversy. The X,Y,Y chromosome. Some people have claimed they have found a higher representation of these super males in the prisons. Suppose this were true. Suppose we actually found that the X,Y,Y super male was more aggressive, more likely to be engaged in antisocial behavior. If this were true, would we opt for gene screening to prevent their birth or gene therapy for treatment?

The answer, I think, is a much more social than biological question, depending upon where you are in the society.

The rate of incarceration for whites is 65 per 100,000 in this country. For blacks, it is 560 per 100,000. Our prisoners are getting darker and darker every year. Without a careful monitoring, as we see the link between genetics and crime, as we have seen in various articles in the National Academy of Sciences and the New England Journal of Medicine—I think, it was within the last year—the crime gene link is not beyond one's paranoid fantasies to see how people would connect the two and talk about how certain gene therapies, as opposed to gene screening, might have an effect on social use.

We need, in sum, disease-by-disease policy planning, talking about gene therapy and gene screening for social groups; risk-population with a high representation in policy planning, and, finally, we need social monitoring devices to trace the implications which are social and political of the screening and of these gene therapies.

[The prepared statement of Mr. Duster follows:]

TESTIMONY
before the
SUBCOMMITTEE ON
INVESTIGATIONS AND OVERSIGHT
of the
COMMITTEE ON
SCIENCE AND TECHNOLOGY
U.S. HOUSE OF REPRESENTATIVES

NINETY-SEVENTH CONGRESS

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Troy Duster

Gene screening and gene therapy have the capacity to lessen human suffering for individuals and for the families of individuals suffering from chronic health problems related to genetic disorders. Others who have testified before this committee are better equipped than I am to chronicle the positive uses of these real and potential developments. I have not come here to argue either for or against screening or gene therapy as it relates to these individual uses.

My purpose is rather to draw closer attention to the social and political issues that can inadvertently emerge at a quite different level than individual choice (of the use of the new genetic technologies). Certain developments might otherwise escape notice if we direct all our energies to the level of the bio-medical, the genetic, and the individual.

Most of my remarks will be based upon genetic screening, though much of what I say here will apply to gene therapy and the application of the new technologies. The link between genetic screening and gene therapy is in part through application of technology. In part the link is suggested by the question: Should we screen in order to prevent the birth of an infant with a genetic disorder, or should we develop gene therapies to treat those born with such defects? Or, if we do both, where would resources be best allocated?

It is not merely a futuristic fantasy that some citizens of this nation command sufficient technology to determine which fetuses are "defective" and which are not, in time for early termination of a pregnancy. Presently, only women over 35, or those with a family history that places them at a greater risk for having a child with a genetic disorder, are likely to be screened.

But the technology is moving rapidly, and we should consider what will happen when every women of child-bearing age has the information about the "defects" of the fetus in her womb. Already, colleagues at the University of California at San Francisco have developed a technology that does not require karyotyping for the detection of sickle-cell after amniocentesis. Chang and Kan (New Engl J Med 307: 330, 1982) have reported a method by which DNA from fetal cells obtained by amniocentesis can be assayed to determine whether the fetus is a sickle cell anemia carrier, or has sickle cell anemia.

The test is sufficiently sensitive that the cells can be used as obtained, without the need for growing them in culture. This reduces the time needed for the test. The techniques involved are all routine in terms of current DNA technology. Research being done on other diseases caused by single genes suggests that similar methods will become available for some other such diseases fairly soon. It seems likely that within 10 years comparable tests will be available for a considerable number of diseases or syndromes. It also seems likely that by then prospective parents could be offered a battery of tests screening for, say, the 10 diseases for which their fetus is at greatest risk.

As a nation, we have not faced up to the implications of what will happen when technological developments and innovations make the present amniocentesis obsolete: when we get a test that is so benign and low-risk, so streamlined and inexpensive, that it will be available to all pregnant women. It is almost inevitable that such a test will emerge from the new technology, with results available in time for first trimester abortion.

When that day arrives, members of different societies and sub-societies will decide quite differently on this "biological" or "personal" question of birth. It is a development that will fundamentally alter the debate now engaged by right-to-life (anti-abortion) lobbyists versus those who would leave abortion as an option for individuals. Presently, the issue revolves around claims of the right of the woman to decide about child-bearing *per se*, or around demands for state prohibition of abortion across the board. But with detection of birth defects *in utero*, we enter a new age in which the level of conceptualization shifts. The new question becomes not simply whether to have a child or not, but *what kind of child to have*.

For the first time in human history, a prenatal decision about the negative or "defective" attributes will be available to ordinary citizens on a routine basis. When such tests are generally available, there will be all the appearances of individual or personal decision-making. However, these decisions are far less "individual" than we frequently realize, more the product of subtle social processes that define, shape and color the content of our thought. On this seemingly personal and natural matter, Jews will typically act one way, Chinese another, Arabs, Malaysians, Russians, English, and blacks yet another, perhaps males and females still another... each in a way that is sufficiently patterned as to render an explanation of individual decision-making inadequate.

Here is an example: The ratio of males to females at birth is approximately 104 to 100. This is an historic constant, because prenatal intervention around sex preference so far has been minimal. But we know from cross-cultural studies by social anthropologists that almost all known cultures have a sex preference for the male infant. Given a choice, "individuals" would skew the birth ratio of 104 to 100 upwards to a much higher figure. Individuals, of course, are the carriers of the cultural biases about sex preference, and their actions would reflect this. A parallel conceptualization could be provided for what would happen for infants with birth defects. If select social groupings are enthusiastically entering into this realm of gene screening and gene therapy more than others, there will be a systematic (as opposed to random) re-distribution of birth defects.

The following case reveals how social researchers might look differently at the patterned variations in the ways in which different parts of the society use these technologies.

California State Funding for Amniocentesis.

In 1976, the California State Legislature passed a bill requiring the Department of Health to set up a three-year pilot program of prenatal testing for inherited disorders by means of amniocentesis. Thirteen medical centers joined the program, each affiliated with a medical school. Because amniocentesis provides some mortality risk to the fetus (perhaps 1 in 150 depending upon the study, and probably related to the experience of the physician), the procedure is restricted to women with select characteristics which place them at greater risk for having a child with an inherited disorder. The state health department set out the following criteria, restricting amniocentesis support to:

1) Women 35 years of age or older.
2) Women having had a previous Down Syndrome child or a child with any other genetic disorder.
3) Pregnancies where one parent is a translocation carrier.
4) Women who are carriers of a sex-linked disease.

5) Pregnancies where both parents are carriers of an autosomal recessive trait.

6) Pregnancies where the parents have a previous child who has a neural tube defect.

In the first two years of the program, 6,643 amniocenteses were performed, resulting in the detection of 171 (2.6 percent) genetically abnormal fetuses.

Who Uses the Service of Amniocentesis?

We have already noted that most of the women who have used the state-supported program for amniocentesis are over 35. As we can see from Table III, only about 5 percent of women who bear children in California bear children after the age of 35. Those who do so tend to come from families that have delayed child-bearing as a matter or choice. This tends to be the family where the woman has a professional career that she has pursued during early child-bearing years. Thus, the women who show up for amniocentesis tend to be much more likely to come from the higher social and economic strata (refer to Tables I and II). The average cost per patient is approximately $550. Generally, the state bureaucracy asked that each person contribute about $200 to this figure. The average family income of women using prenatal diagnostic services in California during the two-year period under discussion was $26,300, while the median income of a family of four in California at the time was $18,900. Table I indicates the more precise utilization of services by income distribution.

Individualized vs. Group Responses to Gene Screening

This raises the issue of the individual vs. collective response to a genetic screen. Where the genetic screen overlaps racially or ethnically distinct groups (as with sickle cell for blacks or Tay Sachs for Jews), it is possible to see political mobilization around a disease that is "their own" -- a risk population that can see its health interests because of social and cultural factors which bind them. It is equally significant to attend to latent issues when there is no overlap between the genetic screen and socially identifiable groupings.

Here is an illustration: There is some evidence that people with northern European ancestry (among them northern Germans, Danes, Swedes, and Norwegians) are at much greater risk than the rest of us for an inborn deficiency of serum alpha anti-trypsin, and are vulnerable to chemical agents in the industrial workplace that could trigger emphysema and chronic bronchitis. If in the next decade the new technology for detecting such inborn errors was to permit such a genetic screen, a social analyst would have solid basis for predicting a quite different pattern of mobilization than we have seen for sickle cell, Tay Sachs, or beta-Thalassemia.

European-Americans of north German and variable Scandinavian ancestry do not comprise a social grouping identifiable and known to each other. At the workplace, they are, for purposes of interest group potential mobilization, far too isolated and fragmented. When a small percentage is identified as vulnerable to emphysema due to a genetically related deficiency, neither the workers as a collectivity nor the individuals identified will see it as in their interest to mobilize as a group. The victims will be seen as isolated and particular cases with a personal problem. There is an interesting dialectic here, because the isolation of these persons genetically screened is explicable by social and cultural developments.

Rather than seeing a social reaction to the new genetic screen, then, as we have seen with blacks over sickle cell, the wave of the next period could well be the passive, individualized acceptance of a "personal" problem of a genetic deficiency that does not permit one to work on certain jobs. This would be a reversal of the trend of the last decade of the genetic screen, where personal problems have been reframed as social problems. The new genetics may help take social problems and turn them into personal problems.

As soon as the current administration took office, the new director of the Office of Management and Budget recommended actions that would reduce monitoring and enforcement of worker health and safety by the Occupational Safety and Health Administration. Among other things, it was recommended that new standards on worker exposure to asbestos (a known carcinogen), chromium, cadmium, and grain elevator dust be deferred or drastically modified. If the government retreats from this arena, the interests of industry are likely to be in a one-sided battle with the interests of fragmented and atomized workers who have individual chromosome breakage, or long-term genetic damage of a variety of sorts.

Unique Policy Issues with Genetic Disorders and Health Planning

It is the role of the state to protect its citizens against contagious and debilitating diseases. As a nation, we have had great successes in handling the public health issues around tuberculosis, many venereal diseases, and smallpox. But genetic diseases are contagious in the very limited sense of the transmission of genes between two adults to their offspring, a matter previously dominated by an overwhelming emphasis on personal choice. Here we have an important example of potential tension between the individual and the state (or its representatives) that may well occur over which kinds of babies can and should be born. This, too, is not as futuristic as it may appear at first glance. When the state is footing a good part of the bill for gene screening, legislators want a demonstration that it is cost-effective, that these programs demonstrate in monetary terms that there are savings. For instance, in California, the State Department of Public Health defends itself for supporting amniocentesis centers by arguing that they reduce the number of births of children with Down Syndrome, thereby reducing costs to the state in the long run.

Individuals, on the other hand, may have a variety of reasons for deciding to make the choice to have a child on grounds other than pure monetary interests. Among others, social philosophers, humanists, religious leaders, and political theorists through the ages have pointed to the potential conflict between the individual and the state. The reason why it is worth taking special notice of the potential in this arena of genetic screening is that it could easily take us by surprise as a nation. But this is not the only arena of special concern around gene screening for public policy.

Unlike contagions, genetic diseases are ethnically and racially linked. That is, while smallpox crosses over all ethnic and racial boundaries, most genetic diseases are found primarily in populations that have intermarried for generations and centuries. To mention but a few of the better-known examples, Tay-Sachs disease is empirically associated very strongly with Ashkenazic Jews, Sickle Cell disease with blacks, and Thalassemia with Mediterranean peoples. Cystic Fibrosis is rare among Asians, and twice as likely to affect whites as it is to affect blacks. White children get Spina Bifida twelve times more frequently than Japanese children, but the Japanese have the highest incidence of Cleft Lip and Cleft Palate of any ethnic or racial group (Apgar and Beck).

This linkage of genetic diseases and race and ethnicity means that laws which mandate screening for such disease already provide examples of the practice condemned by the Nuremberg trials of German war-criminals after World War II: namely, the Third Reich's practice of specifying ethnic and racial groups in legislation by the state. Coming in the wake of the genocidal annihilation of Jews and Gypsies, the Nuremberg trials served to dramatize the moral consensus of the War's victors against the scapegoating of a single ethnic or racial group by state power. Before and during the days of Nuremberg, moreover, anthropologists in Western nations declared with authority that "race" was merely and only the social construction of the unenlightened, the prejudiced, and the malevolent. Today, we are forced to be more cautious in our formulations about the biological, social and cultural linkages of race and ethnicity, as laboratory scientists learn more about the genetic code and gene pools. The dilemmas posed to societies which espouse equality before the law for their citizens will be sharpened by the designation of ethnic and racial groups to be screened genetically as a matter of law.

Genetic screening acquires another social-political dimension through the social stratification of ethnic/racial groups. Some societies are relatively homogeneous, ethnically and racially, as with 19th-Century Sweden. Such societies tend to experience clear estate and class stratification. But, in those societies where there is considerable ethnic/racial heterogeneity, social stratification typically parallels and overlaps the ethnic and racial groupings. Such facts will serve to distinguish genetic screenings from all previous health screening, since--quite in contrast to mass screening for contagious diseases-- it cannot be made appealing to all groups for the common or collective good. Being linked to ethnic/racial groups which are socially stratified, genetic diseases also are socially stratified, not merely biological, socially "neutral" characteristics. The same is true, inescapably, for medical and legal measures to deal with them.

Because genetic diseases both distribute and manifest themselves differently in the population, particularized screening and prevention procedures are necessary to equalize citizens' treatment before the law. This is true, not only because the diseases themselves differ, but because the groups primarily affected by them are different also--historically, culturally, and in their positions on the hierarchies of political and economic power. Such facts sharpen the difficulties which decision-makers face in answering the hard questions about how scarce national resources are to be spent: Which diseases are most important? Which groups are most deserving, or most needful, of government-supported action?

With increasing knowledge of people's genetic make-up, actuarial risk categories can be made smaller and more strictly defined. Those who happen to have a detectable genetic disease or a detectable probability of having affected children will be charged higher premiums or may well become uninsurable. Thus the benefits of spreading costs and risks over a large, heterogeneous population will be lost. Here is a likely development for insurance company policy provisions: If a parent or couple is at risk of having a child with a genetic disease that is detectable by amniocentesis, the company will pay for the costs of amniocentesis and of therapeutic abortion if the fetus is affected. However, if the parents decline amniocentesis, or if they decline abortion if the fetus is found to be affected, the insurance will not pay for medical costs if an affected child is born.

Finally, one of the most important things to say to the lay public about genetic diseases is that they are highly variable. They range from minor inborn errors of metabolism to major problems that can cause physical deformities and threaten life. Even more difficult for law and public health "policy", there may be high variability in the clinical expression of a particular disease. It is therefore difficult to have a general policy, except one that permits for high flexibility, by disease and for a specific population at risk for that disease.

Conclusions and Recommendations:

1. Legislation and Programmatic Planning By Disease

Because of the high variability of genetic diseases, and the fact that they affect groups of the population in systematically different ways, law and policy should be made specific for each disease. In some instances, postnatal screening is indicated; in others, funding should be made available for *in utero* screening; in still others, carrier screening makes the most sense.

2. Victims and/or Risk-Populations should be Represented in Policy Matters

Much more than in previous health screening for contagious diseases, or the administration of therapies, the issue of "who screens whom for what purpose" becomes central to the success or failure of the screen, to voluntary compliance, and to the implicitly coercive role of the state. Setting up a screen implies that the "screened for" are unwanted.

Since the Nazis gave it such a bad name, eugenics is not on the tongue of many people. Making good stock, or fine Aryan babies is still very much anathema. But the elimination of "bad babies" is the meaning of a genetic screen. A racially and culturally homogeneous nation might come to some working agreement about what makes for bad babies. In a heterogeneous mix, the public forum for this debate needs to be vigorous and informed, not just by modest levels of technical knowledge about genetic or microbiological developments, but about the role of power and social location in the determination of that knowledge and its application.

Almost all of us will applaud the technology that permits us to determine whether a fetus has Tay-Sachs, but the cutting edge of consensus begins to fall away around "policy" for controlling levels and kinds of sickle-cell anemia and levels and kinds of mental retardation. Quite simply, we must face the question, "When do we shut the backdoor to eugenics?" For these reasons, there should be provided by law some form of representation (for the population at risk) in every program of genetic screening or gene therapy. The Tuskegee Syphilis Study, funded by the National Institutes of Health from 1932-72, is still too fresh in our memory for any cavalier dismissal of the fact of differing interests of the bio-medical establishment and select parts of the population. Representation of the interests of those affected might have reduced the level of syphilis in those 400 black males in Macon County, Alabama, who were allowed to suffer and die as "controls" for purposes of research.

3. Integrate a Social Research Monitoring Device into Any Large Scale Government Support for Gene Therapy/Screening

As indicated in the earlier testimony, some social groups are well-located in the society, and their "genetic destiny" or genetic screen is heavily influenced by this fact. Other kinds of gene screening and gene therapy research may serve to further individualize and fragment people, undermining their capacities to come together collectively to protect their health or economic interests. Social research is no automatic resolution or counter to this problem, but it is one of the ways attention might be brought to these matters, and any inroads or increased assurances that potentially empower newly created individualized victims should be buttressed.

In particular, there should be a commitment of resources to social science research for studies of the differential impact of genetic screening and gene therapy on different populations. The government should not fund gene therapy research without a built-in device to monitor the social implications of this research. Scientists of any field have narrow career interests. Biological scientists are no exception, and we should not expect detached objectivity of them. This observation is particularly important to make in the present period, where under the thin disguise of economic policy the OMB is using a partisan political axe to support "genetic thinking" about social issues. The full implications of this are elaborated in testimony given at the hearings held by Congressman Dellums at the University of California, Berkeley, in June, 1981. (Summaries are available through Congressman Dellums' Office.) If as a nation we embark upon a fast-forward pursuit of gene screening and gene therapy without close attention to its social implications, we are opening up a backdoor to eugenics while "no one is looking."

4. Resources for Education, Not Just Re-Assurance

Everyone is in favor of more education for these matters of genetic technologies. However, as a nation, we should confront the fact that these new technologies have both benefits and costs. Thus while we certainly need education, the question is, what kind of education?

Is it to be an education for reassurance, by which research scientists and a bio-medical elite simply re-assure a skeptical, ignorant, and fearful population that there is little to worry about in genetic manipulation -- that there is risk in anything? Or shall we opt for an education in which the members of society are informed of the real risks and costs of these new technologies as well as their potential benefits?

One of the risks that I would like to call to your attention is the latent social definition of "good babies" that is a fundamental feature of any elaborated genetic screen or gene therapy. During the last eighteen months, the National Academy of Sciences and the New England Journal of Medicine have published articles that put forth genetic explanations of mental illness and crime. The incarceration rate for whites in the United States is 65 per 100,000. The incarceration rate for blacks is 560 per 100,000. It requires no great leap of imagination for a lay public to link these matters, with a not so subterranean longing for a genetic screen to help make these problems go away. Without a certain kind of education for risks, we may be overly inclined to see "genetic disorder" when there is an implicit notion of "social disorder" inherent in an expanding genetic screen.

TABLE I

INCOME Level	% DISTRIBUTION OF INCOME for California*	% DISTRIBUTION OF Women Receiving Amnio-Centesis in California Prenatal Diagnosis Program, 1977-78
$ 6,000 & Under	1.2	6.5
7,000 - 10,000	12.7	9.9
11,000 - 15,000	21.3	14.7
16,000 - 20,000	28.9	22.0
21,000 - 35,000	27.8	30.6
36,000 & Over	8.1	16.4

*California State Franchise Tax Board 1976 Annual Report for the 1975 Income Tax Year

(From Report to California State Legislature,
(Genetics Disease Section, January, 1980)

TABLE II

LAST PAID OCCUPATION OF MOTHERS RECEIVING AMNIOCENTESIS COMPARED WITH 1970 CENSUS FIGURES FOR CALIFORNIA WOMEN

OCCUPATION	NUMBER	PERCENT	PERCENT OF 1970 CENSUS
TOTAL	6,643	100.0	99.9
Professional, Technical	1,992	30.0	15.8
Managers, Officials	274	4.1	4.4
Clerical, Sales, & Kindred	1,458	21.9	44.2
Craftsmen, Foremen, & Skilled Workers	134	2.0	1.5
Operators, Semi-Skilled	234	3.5	9.9
Service Workers, Farm Owners	351	5.3	17.0
Farm Laborers, Foremen	52	0.8	0.6
Members of Armed Forces	2	0.1	-
None	781	11.8	-
Not Reported or Declined to State	1,365	20.5	6.5

(From Report to California State Legislature, Genetics Disease Section, January, 1980)

TABLE III

AGE OF MOTHERS RECEIVING AMNIOCENTESIS COMPARED WITH CALIFORNIA BIRTHS, 1977

AGE	NUMBER	PERCENT	CALIFORNIA BIRTHS*
TOTAL	6,643	99.9	99.9
15	0	-	0.2
15 - 19	43	0.6	15.2
20 - 24	241	3.6	34.3
25 - 29	417	6.3	30.5
30 - 34	730	11.0	14.7
35 - 39	4,206	63.3	4.1
40 & Over	943	14.2	0.8
Unknown or Declined to State	63	0.9	.01

*California Vital Statistics Birth Records, 1977

(From Report to California State Legislature, Genetics Disease Section, January, 1980)

Mr. GORE. Thank you very much.

Dr. Elena Nightingale, senior scholar-in-residence, Institute of Medicine, National Academy of Sciences, and visiting associate professor of social medicine and health policy, Harvard University School of Medicine.

Dr. NIGHTINGALE. Thank you.

I am pleased to have this opportunity to participate in the third day of these hearings, when the subcommittee is considering the societal concerns associated with human genetic engineering or manipulation.

I am a physician and a geneticist. I have been interested in what is now called genetic engineering for the past 25 years; first, as a laboratory researcher in the field of DNA-mediated transformations in bacteria and in mammalian cells, and, much more recently, as a member of the Recombinant DNA Advisory Committee—RAC—of the National Institutes of Health—NIH. In addition, I have been counseling patients with genetic problems at the Georgetown University Hospital here in Washington since 1974. My interest in this field, therefore, encompasses several perspectives: laboratory science, public policy, and patient care.

Unfortunately, I was away since last Thursday and was unable to hear what went on either at these hearings or those of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research last Friday, so I will abbreviate my written statement, because I think some of what I was going to say has been covered adequately.

You have already heard that our knowledge about genetics—from molecular to human—has increased remarkably in the last decade, especially as a result of development of recombinant DNA technologies. Perhaps the most important benefit of this research has been the development of an understanding of the genetic process. Such understanding will enable the development of a variety of approaches toward the prevention, diagnosis, and treatment of the more than 2,000 genetic diseases so far described. These diseases may be rare individually, but in the aggregate are one of the leading causes of death and disability in the young. It is imperative to our welfare that such research, at the basic and applied levels, continue. Nonetheless, genetic engineering methods intended for the prevention of death and disability and I am aware of difference set of manip germ or somative cells, could also be used eventually for the genetic manipulation of characteristics or traits of human beings that are viewed by some as undesirable, even if they are not associated with disease and not only re behavior but also as traits such as gender—which we can manip. Because of the great potential for unintended deleterious—because of inherent uncertainties—effects and for misapplication, the ability to change the human genome—application to germ cells—by new techniques will require continuous scrutiny, evaluation, and discussion.

My experiences with the recombinant DNA Advisory Committee—where, at times, experts would change opinions after open discussion of questions that initially had not even been viewed as questions, but as facts—and where the single-minded desire for unhampered research was often obvious—lead me to the conclusion that some kind of oversight mechanism for future research and its applications in this field is not only desirable but necessary. Applications of genetic engineering to man have wide societal and personal, intimate implications, and cannot be left to researchers or practitioners alone no matter how well-meaning. So far, unintended laboratory hazards of recombinant DNA research have been subject to oversight. Institutional review boards, whose procedures are prescribed on a Federal level, function locally to protect human subjects of research. But—and this is a crucial point—there is no process or mechanism for dealing with clinical applications of genetic research to man, a deliberate process with great potential for benefit and risk. And, by and large, the recipients will be the unborn, infants, and children, who cannot speak for themselves. The implications of genetic engineering for health care in early life need to be monitored by persons other than those interested in promoting new technologies. As Mr. Duster says, equity of access to services—if they are good—is a public health problem.

There are certain features about the history of the Recombinant DNA Advisory Committee that are relevant here. The "first generation RAC," to use the terminology of the former Director of the National Institutes of Health, Donald Fredrickson, was a group composed primarily of molecular biologists with some other scientists. The committee was advisory to the Director of the National Institutes of Health, but some of these experts, although extremely well informed, were themselves using the techniques in question or were very interested in the promotion of their use. In addition to the peer review, the NIH Directors Advisory Committee, which had within it both scientists and laymen, served as a second, broader tier of review. After 2 years, then-Secretary of Health, Education, and Welfare, Joseph Califano, established the "second generation RAC." This group was composed of one-third molecular biologists, one-third scientists in related and relevant disciplines, and one-third persons from public health, law, consumer affairs, and public policy. This broader group combined the functions previously performed by two groups. It succeeded remarkably well in spite of apprehensions of the technical experts, both in and out of government. The public members helped to keep the debate honest and asked relevant questions that would have been overlooked by the experts or assumed by them to have an obvious answer. As Dr. Fredrickson pointed out, the layman in the midst of experts can "observe the experts to see if they appear to be listening to each other and paying some attention to the evidence." The second generation RAC is still in place. In my view, the RAC has been successful in permitting recombinant DNA research to progress at an acceptable rate while guiding and maintaining oversight over this research to avoid biohazards. Voluntary compliance with the NIH guidelines has been the rule in industry. The institutional mechanism of a broadly based oversight and review committee housed within, and with support of the NIH, and with the collaboration of other Government agencies through the interagency group, has served us well and should not be discarded lightly. Rather, as the applications of genetic research reach out into the human domain to a greater and greater extent, the RAC might be used as a point of departure for thinking about what kinds of oversight groups might be put in place that would go beyond prescribing the conditions and procedures for conducting research safely to developing guidelines for appropriate human clinical application.

I have thought about what some of the desirable characteristics of such an oversight group might be. They are offered as starting points for discussion. These include:

A broadly based group that includes a critical mass of experts in relevant biomedical and clinical disciplines as well as persons experienced in public health, law, ethics, religion, consumer affairs, and public policy.

The group might have panels, each dealing with a technical subject. These panels would not only have greater representation of the necessary experts, but would also have public members within them. The panels' reports, policy analyses, and recommendations would then be brought to the broader committee for review.

The group should develop guidelines, recommend policies, and perhaps even function in a quasi-regulatory manner.

It should be a balanced group of thoughtful people not subject to political pressures or sudden changes in composition for political reasons.

The work of this group should be conducted in public. The Recombinant DNA Advisory Committee meetings, except for those that deal with proprietary information, are open to the public, and members of the public are invited to comment and to participate. This openness is invaluable, I believe, in having the recommendations of the committee be credible with the various interested parties. Furthermore, it serves an important public education function, at least in part, because of frequent reports in the press on the proceedings, issues and debates.

It could be responsible to a high level officer; for example, the Secretary of Health and Human Services, or to the Assistant Secretary for Health, rather than to one agency—such as the NIH, whose mandate is more circumscribed, is appropriately an advocate of science, and is not primarily concerned with patient care. Or—and this possibility should not be considered lightly—it could be free-standing and separate from Government altogether.

The group should have participation by relevant departments of the Federal Government and the private sector, including, as appropriate, organizations such as the American Association for the Advancement of Science, the American Medical Association, and the Institute of Medicine/National Academy of Sciences.

The need for, and constitution of, the group should be reviewed with a reasonable periodicity, such as every 2 to 3 years.

It is important that such a group be able to move swiftly if problems develop. For example, the case of Dr. Cline, whose testimony you heard this morning, was handled by the National Institutes of Health with reasonable dispatch and, from what I can tell, with fairness. This was because the guidelines for research with recombinant DNA were already in place and measures to be taken in case of violation were already outlined. In the absence of guidelines and of an RAC to formulate and update them, it would have been necessary first to put in place a mechanism for dealing with the problem and only then to deal with it. It is this kind of incident—to be sure, so far, rare—that reinforces my conclusion that since we are reaching the technical possibility of manipulating human genetic material for good and therefore ostensibly also for unintended or intended harm, it becomes imperative to study thoroughly what institutional mechanism could be devised to have balanced oversight of the application of genetic research to man.

It is inappropriate for one person to glibly write a prescription for an oversight committee with such important and complex tasks. What is needed is an innovative mechanism to deal with the clinical, ethical, and societal implications of genetic engineering as applied to man. It is important to ask, "How could a body be constituted and housed so that it would have competence in science, medicine, and public policy, and the ability to make recommendations and to function—if appropriate—in a quasi-regulatory role—such as the Recombinant DNA Advisory Committee has done? To whom should such a body be accountable for maximal effectiveness?"

The Recombinant DNA Advisory Committee, which worked well for its more limited scope, might perhaps be reconstituted—a third generation RAC, in Dr. Fredrickson's words—and based within the Department of Health and Human Services at either the Secretarial or Assistant Secretary for Health level, so that prevention, diagnosis, and treatment of diseases, and other applications, would be appropriately considered.

The National Academy of Sciences/Institute of Medicine could possibly be the institutional home for an oversight committee, provided that the committee was able to maintain its independence from a review process established and necessary for other purposes. While able to convene an appropriate membership for a broad oversight committee, the NAS might be perceived as an advocate for science and, therefore, not broad enough to accommodate the relevant clinical aspects of the problem. The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research might perhaps be reconstituted for this purpose, but it should be insulated from political pressures.

The Office of Technology Assessment, as now constituted, delineates options but does not make recommendations. The possibility of its serving such a function might also be explored.

In summary, I am convinced that continuous oversight of the applications of genetic research to man is both desirable and necessary. Important questions to be resolved that will require serious study are the sponsorship of the group and to whom it should be accountable.

This is the time to begin careful and thoughtful consideration—on a national level—of the construction of oversight mechanisms in the field of human genetic engineering. While it is impossible to predict the future—progress has been at a pace far quicker than envisioned even a few years ago—human genetic engineering will be upon us, and rather than have events overtake us, we should be prepared to deal with its varied and long-term implications for the benefit of the involved generation and subsequent generations as well.

Mr. GORE. Thank you. That is really very helpful. I appreciate all the statements.

I have a number of questions, and I will try to run through them quickly because of our time constraints.

Dr. Davis, you seem to be less troubled by a lot of these developments than others. Yet you say in your statement that cloning of people would raise such serious moral problems that you would oppose it. On what grounds would you oppose it?

Dr. DAVIS. I would oppose it first on the grounds that deciding how to handle it would create too many social conflicts. I might personally like to see a Mozart or another Newton, but other people would have different preferences. But how do we decide in a society which people are going to be cloned? Is it going to be somebody who can afford to be cloned? The choice of which to be cloned is not clear because the criteria——

Mr. GORE. Problems of access similar to the ones Dr. Duster has raised with respect to gene therapy?

Dr. DAVIS. Yes. Second, I think the moral responsibility for making a person who is going to be a carbon copy of somebody else would be enormous.

Mr. GORE. Sort of like playing God.

Dr. DAVIS. Well, in a way. It might be a little more precise to use the phrase "identity crisis."

Mr. GORE. The definition of what we mean by "human being."

Dr. DAVIS. Yes; but even more the definition of an individual human being. People growing up have trouble in the teen ages establishing their identity. For a carbon copy of a parent the problem would be much greater. A third objection is that our species benefits greatly, in terms of both survival and culture, from its genetic diversity; if cloning were done on a large scale it would lessen that diversity and would create enormous social problems.

If cloning of mammals should become possible I can imagine that society some centuries hence would have evolved in such a way that it would be cloning people; and I don't think we can legislate now for the next thousand years. But at present I don't think we could handle that power wisely.

Mr. GORE. Would you then place the burden of proof on scientists who would propose to conduct such a procedure? Would you put the burden of proof on them to give us some idea of how these many questions would be answered and to give us some assurance this awesome power could be used without untoward consequences for our social fabric and our understanding of ourselves as human beings? Would you place the burden on the scientist to give some hint of an answer to those questions before allowing the scientist to proceed?

Dr. DAVIS. I would say first of all I think cloning from adults, as I noted in my prepared statement, is not very likely.

Mr. GORE. It is unclear. There is an enormous amount of research going on right now in the gene activation mechanisms. It is quite true as cell differentiation continues beyond the embryonic stage genes lose their capacity to express themselves. There may be other changes you are referring to of which I have no knowledge whatsoever, but it doesn't seem unreasonable to suppose that it is possible for a researcher to find some way to reactivate or to recapture the information that is retained in the gene and find some way to express the genetic information that is contained as residue, even in the cells of adult individuals.

Dr. DAVIS. I would agree with you entirely if the differentiated adult cells had exactly the same set of genes as the zygote. And 10 years ago it was pretty dogmatic that in all differentiated cells the genes are all there but their expression varies. Any cell on the average is believed to express around 10 percent of its genes and repress the other 90. However, recent experiments have shown that the set of genes in the cell are not that stable, and there are indications—not proof—but there are indications that slight differences too subtle for us to define yet chemically may occur. And the main reason is——

Mr. GORE. May occur in all the——

Dr. DAVIS. In the adult genes.

Mr. GORE. In all the cells?

Dr. DAVIS. Let me state you briefly what the nature of the evidence is. In efforts to clone by nuclear transplant, which so far has been successful only with cells from frog embryos, there have been a great many efforts to do the same with nuclei from adult frogs, and in no case has the cloning been successful.

What happens is that the nuclei from an adult frog cell——

Mr. GORE. It has been done in other animals as well.

Dr. DAVIS. Not by nuclear transplant from differentiated adult cells.

Mr. GORE. But cloning of a slightly different kind, which is still technically cloning, has been done in other species.

Dr. DAVIS. There are two kinds of cloning, from embryo cells—twinning—or from nuclei at later stages. Let me stick with nuclear transplant, because if you want to copy an already tried, tested and observed adult, whether of prize livestock or of a person, you have to start with nuclei from somatic cells from that adult.

Mr. GORE. Not necessarily. We heard testimony in an earlier series of hearings from experts in animal husbandry that there is a possible procedure to replicate or clone by a technique not involving nuclear transfer but the one you describe in your statement——

Dr. DAVIS. Separating the cells.

Mr. GORE. Separating the cells at a very early stage of cell differentiation, replicating precisely the embryo, making many clones of it, freezing all but one, allowing one representative of that group to grow to maturity, assess the genetic characteristics and then make a decision as to whether or not to implant other identical specimens.

Dr. DAVIS. Yes; you are correct.

Mr. GORE. It is technically possible. That is within the capabilities of science where human beings are concerned right now.

Dr. DAVIS. You are well-informed, Mr. Gore. You are absolutely correct on that—though it would still be starting with an unknown embryo and later deciding that that individual deserved to be selected for cloning.

Mr. GORE. Would you prevent that?

Dr. DAVIS. I think I would, for the reasons that I indicated in rejecting human cloning from adults. The social problems in the present state of our knowledge are too great. But you asked me a question about whether I would like to have scientists have the power to decide that.

Mr. **Gore**. Whether you put the burden on them to answer the societal question.

Dr. **Davis**. I would say absolutely no. It is not a scientific question.

Mr. **Gore**. If you would prevent them from proceeding before the questions are answered, then, it seems to me in a very real sense the burden is on the scientist.

Dr. **Davis**. Well, let's back up a little bit. Before one did that, started cloning human beings, one would be cloning other mammels. I am not opposed to the cloning of mammals for agricultural purposes. It might improve the food supply of the world. So the research that would enter into learning how to clone in mammals, if it should become possible, is something that should not be stopped. The application of the results of that, if it should be possible for human beings, is very much a societal judgment. I don't think it would be at all appropriate for scientists to make that judgment, because it is a value judgment, and in principle, there are no objectively correct answers to such questions. Science may be able to help predict the consequences of alternative answers, and further research may improve the predictions: but research still cannot provide a correct answer, and so these are not questions to be left to the scientists.

Mr. **Gore**. Let me come back to the central question, because it is curious and instructive to me that you who are known as and have an earned reputation as being sort of——

Dr. **Davis**. Defender of the faith in science.

Mr. **Gore**. Well, OK; that is a good way to put it. It is interesting to me that you would prevent scientists from doing something that is now theoretically within the capabilities of science and that the reason you would prevent them from doing it is because the procedure would raise questions of a moral, societal nature that we don't know the answers to.

Now, you see what I am getting at?

Dr. **Davis**. Yes. In other words, I am capable of seeing complexities as well as simplicities.

Mr. **Gore**. Let me draw a sharper parallel. Many of our colleagues feel exactly the same way about experiments that would alter germ line cells. Even for therapeutic purposes, they believe that the questions raised by that technique, that procedure, are vast and the implications are so large that we don't yet have a good way to even hint at the answers to those questions. And some believe that maybe we ought to slow down on the germ line work until we have a better appreciation of what the answers might be.

That is very similar to what you are saying with respect to cloning. You are saying not that the risks and benefits to individuals would lead you to prohibit it but rather that the profound questions posed to society would lead you to not just slow it down but to prohibit it saying you can't do that.

You see what I am getting at?

Dr. **Davis**. There are a great many similarities. But obviously I believe there are differences or I wouldn't take these superficially apparently contradictory positions. What are some of the differences? First of all, in all these areas I make a sharp distinction between the research that gives us powers and the applications of that research. I would defend the research that gives us the powers because there is such a tight link between the various kinds of research going on. For example, research on putting DNA into embryonic cells is a powerful tool for studying developmental biology.

I can also see applications in agriculture that are desirable. I see a graver moral question when you apply it to human beings. I make a sharp distinction between research and decisions about applications. That is really the main distinction that I make. I think there are some others that slip my mind for the moment.

Mr. **Gore**. That would be fine. If you wish to extend your answer for the record, we will hold the record open at this point, because it might be helpful.

Mr. **Gore**. Dr. Cavalieri, you report that one of the commissioners was asked if he was opposed to intervening in the human germ line and he answered no, but that care should be exercised. One cannot escape the conclusion that the commissioners and the consultants felt that somehow science and technology define progress.

If you were asked whether or not you were opposed to a therapeutic procedure that intervened in the human germ line, would you answer yes or no?

Dr. **Cavalieri**. I would answer that I don't think it should be done.

Mr. **Gore**. You would be opposed to it?

Dr. **Cavalieri**. Yes.

Mr. **Gore**. Why?

Dr. **Cavalieri**. Well, I bring up the obvious point that once you do that you open up an entire area that I don't think we are prepared to handle.

Mr. **Gore**. Sort of the same objection that Dr. Davis and I were discussing earlier with respect to cloning.

Dr. **Cavalieri**. I would suspect it is close to that, yes. There is no way of handling it.

Mr. **Gore**. You would concede that we might develop an ethical framework in which we could handle it, wouldn't you?

Dr. **Cavalieri**. Well, that is possible, and I would say I would like to have public discussion on this. I think hearings such as this are invaluable. I think church efforts should be encouraged, and I think there should be absolute public participation not at an emotional level but on an informed level and an intellectual level, where one can decide in fact what do do about the ethical and moral question.

Mr. **Gore**. I agree with your answer.

Dr. **Davis**. You asked me two questions about the apparent paradoxes in my position, and I failed to answer the one about the germ line. I believe that straight therapeutic intervention in the germ line, correction of a defective cell, but does not present a moral problem any more than gene therapy in somatic cells. I therefore do not believe it needs special surveillance. On the other hand, I recognize that the idea of altering germ cells disturbs many people. I would therefore not object to having a committee explore this topic, and I would try to convince them that this kind of intervention is not dangerous to society if it is restricted to therapeutic purposes. The central distinction still seems to me to be that between therapeutic and nontherapeutic uses.

Mr. GORE. That is a more subtle position. In evaluating the risks of germ line intervention, would you evaluate the risks just to the individual and the children of the individual in question, or would you also evaluate any unforeseen risks to the species as a whole?

Dr. DAVIS. I think the species is not threatened unless some new procedure is carried out on a very large scale.

Mr. GORE. I will use a hypothetical one but there may be a real one floating around where, where a genetic trait that is defined as a disease that is painful and undesirable and we want to get rid of it, nevertheless it has some sort of evolutionary value over a period of geologic time or whatever. I am over my head, but the point is there might very well be unforeseen consequences for humanity as a whole in future generations. Should those be weighed as well?

Dr. DAVIS. Well, you have to balance them against the consequences for human beings. We are dealing here with problems of preventive medicine as well as of evolution, and if we could prevent the multiplication of genes that cause people serious problems in the present world I believe we would have to do so, in the same way that we allow prenatal diagnosis to lead to abortion of a defective embryo.

Mr. GORE. Would you rely on the individual physician to make that assessment?

Dr. DAVIS. I really do, because I don't see it as a major societal problem. On the other hand I see the problem of carrying genetic engineering beyond prevention or therapy of specific diseases as a very serious one.

Mr. GORE. Within the context of the hypothetical example, you have a disease that causes intense discomfort to members of the generation of people now alive. You have some evidence ouside the discipline of medicine that indicates there might be an evolutionary advantage associated with that same gene in evaluating the risk and benefits of the procedure. Would you rely on the physician trained in medicine to fully evaluate the risks to all future generations of human beings?

Dr. DAVIS. I cannot see a risk to all future generations of removing a gene that at present causes a well-defined disease.

Mr. GORE. Maybe the physician involved could not see such a risk either, but there might be such a risk.

Dr. DAVIS. But who is in a position to see it? It would have to be a student of evolution. I am somewhat of a student of evolution but I also have a medical background, including an internship. You may be thinking of such examples as sickle cell anemia or thalassemia, which offer protection against malaria. In parts of the world that are malarial these genes are widespread, because the greater survival of people carrying them exceeds the losses due to the hereditary disease. Seeing what these diseases do to people today, I would say that we would not be justified in deliberately allowing people to continue to suffer from them, simply because of the remote possibility that we might be overrun by malaria again and our society would then benefit from having some people around with these genes.

Mr. **Gore**. Certainly I cannot disagree with that. One of our witnesses several days ago postulated the possibility—Dr. Walters suggested storing genes someplace other than in living human beings in case their value might one day become more apparent. Would you think that might be a prudent exercise?

Dr. **Davis**. That would be a worthwhile thing to do.

Mr. **Gore**. Would you depend upon the individual physician to make that decision?

Dr. **Davis**. It is not up to the individual physician because he deals with only one case of a disease shared by many other people, so somebody else could take another specimen and store the DNA. In other words, I don't think a physician very often has the last copy of a piece of DNA in his hands that he might be destroying by curing the disease.

Mr. **Gore**. But you wouldn't rely on the individual physician who proposed cloning?

Dr. **Davis**. No.

Dr. **Nightingale**. We have talked so far about genetic diseases as if the gene was the sole determinant of the disease, which it is not. If you take the example of gout, gout is not a disease in people with the "gout" genotype in a country with particular dietary patterns—where grains are the staple and little or no meat is consumed. The same genotype in a situation where the diet is based on red meat is a disease. So what you define as a genetic disease and, therefore, what you would do to act on that information depends on the interaction of the genetic constitution with the environment. So the manipulation to correct the disease can come from the genetic or environmental direction. Genetic diseases are not always clear cut and simple. These broader views are best discussed and put to use by more than one person and therefor more than one perspective.

A geneticist might look exclusively at one component, a physician at another, but most genetic diseases are not determined exclusively by the gene or genes involved.

Mr. **Gore**. The same is certainly true of the XYY matter that Dr. Duster brought up.

Dr. **Cavalieri**. I am not quite so sanguine about gene therapy, even in somatic cells. I also think that opens up the doors to——

Mr. **Gore**. In what way?

Dr. **Cavalieri**. A defect might change its perspective, you know. You might want to make an improvement instead of curing a genuine defect. As was just brought out, the genetic defects are not due to genes alone, and so I would welcome, again, wide discussion even at that level of somatic, not just the germ line.

Mr. **Gore**. Thank you very much.

Dr. Duster, you proposed this question: Should we screen in order to prevent the birth of an infant with a genetic disorder, or should we develop gene therapies to treat those born with such defects? Then you discussed that question in terms of the XYY example. What would your answer be?

Dr. **Duster**. My major concern is that the question gets answered differently depending upon one's social position. If we are talking about a population of people in a prison, you can see that their access to levels of power are quite different from those on the outside. Certain populations would have less or more access to power. And my concern is not answering the question, should we screen to prevent XYY? I was pointing to the hidden social potential in treating the issue as if it is one that can be answered by scientists.

Mr. GORE. And you are also treating a very sophisticated subset of the allocation issues, saying that different groups in our society will have different access to these technologies, will answer the questions differently, and will use different approaches with unforeseen consequences.

Dr. DUSTER. Exactly. Well, in particular, they will act as if their interests were linear, that they are concerned with individual human suffering where, in fact, there may be these subterranean social, political, cultural blueprints they are operating from. I could elaborate on that, but there is not much time and I will let it go.

Mr. GORE. Dr. Davis, I wanted to give you a chance to say whether or not the quotation cited by a witness yesterday was taken out of context—if you wanted to comment on that.

Dr. DAVIS. Thank you. It was taken grossly out of context, and in violation of the rules of the meeting. At that scientific meeting, we were all to talk off the top of our heads freely, and when we received the transcript, we were explicitly told that this unedited material should not be cited. There was nothing in there that I have to conceal, but in the context of Dr. Beckwith's citation, it looked as though I were worshipping IQ and not concerned about benefiting people with phenylketonuria.

The actual issue is that phenylketonuria is the classical example of a hereditary disease in which appropriate modification of the environment overcomes a great deal of the defect. It doesn't overcome it all, however, for we cannot control the phenylalanine intake in an infant closely enough to prevent all damage to the brain and some other organs. Accordingly, while dietary control brings most of these children up to a level where they can function in society, statistics show that on the average, they have not reached the mean IQ of the general population. There is nothing special about the IQ test, except it has provided numbers that objectively demonstrate the value of the therapy, and these numbers can also be used to estimate its limits.

In the meeting, we were comparing the environmental approach to the problem with the future possibilities of prenatal diagnosis and eventually, conceivably, of gene therapy. The environmental therapy now available is a great achievement and a boon to the afflicted families, but if prenatal screening becomes available for this disease, parents would have a choice, and it would then be important to provide them with the most accurate possible estimate of the degree of correction possible by dietary therapy. My point was very simple: Because the IQ's of children within a family average closer to those of their parents than to those of the population at large, the measurements of correction would be better if they compared the treated PKU patients with their parents and not simply with the general population.

Mr. GORE. The question raised by the discussion that as quoted there—and I think you have put it into context very well—still the question seems to be, if the technology makes it possible for parents to select the kind of children they want, or with particular traits, based on criteria that are less than—well, that could be viewed by some as essentially whimsical—just IQ, or just hair color—there are differences, of course, but let's take the example of IQ.

Let's suppose it were possible for parents to deal with the question of IQ and they were told that there was a 20-point deficit. Wouldn't it trouble you to see parents decide not to have that child simply for that reason?

Dr. DAVIS. Surely, but that isn't all there is to it. We are certainly not talking about a generalized test for the future IQ of an embryo. We are talking about a well-defined disease, one that can now be considerably improved with therapy. The parent has to make the decision: do I want to go ahead and have a child with PKU, with all its disadvantages, tied to a miserable diet for the first 10 years of life, or do I want to make another try for a child who starts life without this genetic handicap?

Different parents would make different decisions. In that decision IQ provides an index of how far treated children are from what they would have been without that particular unfortunate gene.

Mr. GORE. What about parents who decided to abort a pregnancy because of the sex of the fetus?

Dr. DAVIS. That was discussed yesterday. I heard you say you really didn't want to get into the discussion of abortion.

Mr. GORE. I really don't. Let me rephrase it a different way. What about a parent selecting—it is not as sharp a question that way, and I suppose the answer is not particularly illuminating. If I ask you what about parents selecting the sex of their child, you wouldn't be troubled by that?

Dr. DAVIS. Well, let me give you a slightly more complicated answer than yes or no. With the present situation in our country I think many people would consider abortion for this reason frivolous. I think this is correct. On the other hand, the problem of a world population explosion is going to get much worse. And some people have more children than they really want, in order to reach the sex they don't yet have. My prediction is that some decades from now we might see a society that will say it might be a very good thing to remove that particular incentive for procreation. In that environment I would not be disturbed. I am not, however, proselytizing now for that use of prenatal testing.

Dr. NIGHTINGALE. Actually that situation exists already in China where the one-child family is the goal. I don't know whether this was discussed yesterday.

Mr. GORE. Yes, it was, briefly.

Dr. NIGHTINGALE. There have been reports of infanticide of female children in China already.

Mr. GORE. And large scale abortion.

Dr. NIGHTINGALE. Yes, simply for that reason. This is something that is not for the future but it is here. As far as I know there is no way to tell a particular physician don't do amniocentesis for purposes of gender only. In my practice I don't know that there is any way of preventing that.

Mr. GORE. Would you consider it unethical?

Dr. NIGHTINGALE. I personally do consider it unethical, but some physicians do not and carry out amniocentesis for purposes of gender determination and then do selective abortions. It goes on, there is no question.

Mr. GORE. I consider it abhorrent.

Dr. DUSTER. My understanding is that you cannot not know if you do amniocentesis what the sex of the child is. If it is done, the information is produced. There is law on the topic. Namely, if a physician knows from the lab, that physician is required by several States to inform the prospective mother of the child's sex if the mother makes inquiry, so it is not simply a hypothetical question. The physician is required to inform if the female requests information.

In my testimony as written I indicate there are cross-cultural studies on this topic, and across almost every culture known there is sex preference for the male infant. If the technology were generally available, therefore, I think I would predict there would be a strong change in sex ratios. You only need 4 or 5 percentage points to drastically alter the demographic curve.

Mr. GORE. I read that portion of your statement carefully. You note there is a 104 to 100 male-female difference occurring naturally, and since there is a cultural preference in most societies for male children that could be expected, that ratio could be expected to change if the technology was widely available.

Dr. DUSTER. Systematically.

Mr. GORE. All of you have been very, very interesting and your testimony is very valuable. I wish we had more time to explore it further. I want to thank all of you for your appearance here today and for the contributions you have made.

I would like to welcome all of you to the subcommittee's hearing. Without objection the prepared statements of all witnesses on this panel will be put into the record in full at this point, and I invite you, as with the last panel, if there are portions you feel you can summarize, without doing damage to the integrity of your statements, I invite you to do that.

Dr. Grobstein, welcome. Please proceed.

STATEMENTS OF DR. CLIFFORD GROBSTEIN, PROFESSOR OF BIOLOGICAL SCIENCE AND PUBLIC POLICY, UNIVERSITY OF CALIFORNIA (SAN DIEGO), LA JOLLA, CALIF.; PATRICIA KING, PROFESSOR, GEORGETOWN UNIVERSITY LAW CENTER, WASHINGTON, D.C.; STEPHEN STICH, PROFESSOR OF PHILOSOPHY, UNIVERSITY OF MARYLAND, COLLEGE PARK, MD.; AND DR. BERNARD TALBOT, DEPUTY DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MD.

Dr. GROBSTEIN. I have been listening to the presentations this morning and, of course, there has been considerable referral back to the testimony on the 2 earlier days. It is very clear that it is not necessary to make a number of statements that are in my written testimony. What I would like to do is to hit on certain points that seem to me to be particularly critical, as I understand the present status of the discussion over the last 3 days.

Let me say first I think it is appropriate and essential to launch full discussion of possible needs for oversight over application of genetic engineering in the human species. I think, however, it is important to focus on a couple of words that I haven't heard yet fully defined and which it seems to me important to define. One of them is the word "oversight." I interpret that word "oversight" to imply anything from monitoring through to what one might call rigorous regulation.

While there is a need to have discussion on oversight, I use it over the entire range. I think what is needed are people other than those immediately involved in genetic engineering to maintain a purview in this area and to decide if and when it is desirable for some kind of intervention by parties who are not immediately involved. It is in that sense that I endorse discussion of possible need for oversight.

Second, the simple statement that there is need for discussion of oversight over application of genetic engineering I think it is clear—in the discussion this morning, and apparently also in the discussion of the last 2 days at different times—it is clear that the degree of oversight and the character of oversight may be somewhat different for the various applications that are under discussion. To say one is for or against oversight over application of genetic engineering lends itself to oversimplification.

I think we have to be very much more precise in what it is we are talking about as the subject of oversight, and what we mean by the mechanisms and the purposes of the oversight. I won't discuss the reasons why it seems to me essential to have this kind of oversight. They are addressed in the written statement.

It is also clear such oversight has already begun. I think it important to emphasize that these discussions, unlike those that went on 5 to 8 years ago over recombinant DNA deal with long-term issues and therefore are probably best dealt with by processes of long-term discussion. We do not face an emergency in this area. I don't think anyone postulates there is an emergency, that some catastrophe will occur in the next year or two.

I think what we all recognize is over a period that we can roughly approximate in duration there will be a continuing series of issues that will be presented and that many of these probably require oversight in the sense that I defined; that is, many of them are ones that probably should not be decided by the immediate parties involved alone, although they clearly have an interest and should be involved in an appropriate way.

Now, it seems to me that the questions that are emerging and have emerged during the course of the hearing, as I understand it, are threefold. What is the appropriate deliberative forum to consider this area in all of its complexity and continuing as it probably will to develop over time?

How should such a forum be initiated and constituted?

Third, what should be the initial agenda, keeping in mind that the agenda that it may eventually consider will develop over time and that we can at the moment only see certain questions that need to be addressed. We can sense that others are likely to occur later and it is possible to address questions prematurely if one in addressing those questions is seeking quick answers.

There are a number of questions that were discussed this morning that probably have no sound answers at the present time, in my judgment. The best we can say is we are going to have to keep our eye on them. We are going to have to continue discussing and analyzing them. Maybe down the road when they become pressing we may be better able to deal with them.

It seems to me that our attention should be focused on those matters that are relatively short term. The clearly much longer term issues—we should hope that in dealing with the short-term ones our experience will increase and we will be able to face the longer term issues more effectively.

Now, in that context let me touch on several points that relate to these questions. These points are all addressed in the written testimony, but I am taking them out of context in making these oral remarks. First, it seems to me important to address the matter of the functions of the desirable forum.

Dr. Nightingale has already commented on this fairly substantively, and I think very valuably. Let me just make a few points or highlight a few points that seem especially important.

No. 1, the business of the forum is to bring together the interested parties, the parties who recognize that they have an interest in this particular application for or against.

No. 2, to establish a factual basis, and by that I mean the scientific and technical basis. And I don't mean that it is limited to that. We need to establish the factual basis as it is seen by the parties and as it is seen by suitable experts. That needs to be brought into the forum.

No. 3, there is a need to appraise the conflicting views that exist at the present time, and to seek some means of accommodation among them. It is fairly clear that in this area there are very strongly held conflicting views and that in many instances one policy will not overcome or persuade the other. What is going to be necessary is to find a policy that can accommodate both, and that will take accommodation both in terms of the policymaker and in terms of the independent parties.

No. 4, such a forum needs to determine and to reflected the general community attitudes that relate to this matter, and to provide both in order to obtain information and also to provide a sense of confidence on the part of the larger community—appropriate access by the larger community—to the proceedings within the forum. Everybody cannot participate as an individual. No one should feel, that if they want to sufficiently, they can't be heard.

No. 5, there should be the widest possible dissemination of options with respect to each of the defined issues or applications, the recommended choices as seen within the forum and the rationales for the choices. These all should be available for fullest possible discussion. I should note none of these five relate to regulation in the sense of controlling the situation. That seems to me not to be the business of the forum.

It is necessary, of course, where public action is required to think in terms of mechanisms. But it would seem to me better at this point not to involve that with the deliberative function but rather wait to see what the nature of such control or regulatory processes may be.

No. 2, let me comment on what seems to me to be the kinds of questions that would make up the agenda for the forum, just as preliminary candidates. First, it is clear that the question which has come up repeatedly in discussions here, the first question is, Does this subject broadly define genetic engineering as it relates to the human species? Does this require oversight beyond that already in place for human experimentation?

Now, I submit one cannot give a general answer to that but one must ask a second question, and that is, What oversight, if any, should be provided for the following subdivisions that are currently recognizable with respect to genetic engineering?

(*a*) Under two then, what oversight should be provided for (a) basic research in the area?

(*b*) For genetic intervention in body cells, for designed therapeutic purposes involving the correction of defects.

No. 3, genetic intervention in germinal cells to correct defects. Both of those, of course, have been discussed this morning and there have been discussions about the differences between these, and certainly there is some suggestion that the type of oversight might be expected or that might at best be different in those two occasions.

(*d*) Genetic intervention to improve characteristics rather than to alleviate defects. Now, there has been some discussion about the question of whether or not medical justification, what role medical justification plays. It seems to me that this is a critical issue. It is clear that with respect to medical matters we apply somewhat different criteria than nonmedical ones. And it is clear when we talk about improving characteristics we are certainly boundary at least, if not over the boundary, between what would be called the medical model and other models for intervention genetically. And that boundary certainly needs considerable attention since even within the medical sphere it has never been very precisely defined. Finally,

(*e*) The possibility of genetic modification to reduce rather than to improve the hereditary capability of human beings. In some measure to make human beings less human, which I think is a clearly defined case, as compared with the preceding four.

Now, looking at those matters it seems to me at the present time that the objective should be not to provide rigid rules for dealing with one or another of the cases but to attempt to define guiding principles in dealing with these matters.

If I may, now, I will give some examples of guiding principles that might be adopted now. Not because at the moment I advocate them, but in order to indicate both the kinds of principles and what the set of principles—what "a" set of principles might look like and what kinds of problems such principles might raise.

No. 1, as a principle, basic research findings, should be monitored to anticipate possible applications but no other strictures should be placed on the growth of fundamental knowledge of human genetics.

No. 2, therapy involving genetic modification that is limited to the treated generation, should be conducted largely under health professional codes overseen by institutional commitments. In other words, our existing practice.

No. 3, genetic modification intended or likely to affect succeeding generations should have additional oversight by a group able to assess impact on the human gene pool. Here again one is crossing the boundary of the traditional medical model.

No. 4, genetic modification intended to improve hereditary characteristics of spring should not be attempted in humans pending fuller consideration, and then only for stipulated sanction purposes.

No. 5, genetic modification intended or likely to lead to hereditary limitation of human capability for whatever purpose shall be effectively enjoined.

Now, I would note that there is ample opportunity provided in different instances for laissez faire, essentially, or for additional oversight mechanisms that are not yet in existence, or, for full prohibition when deemed necessary. The important thing is, it seems to me, that the process that is set up should be discriminating with respect to the various kinds of cases or applications that are being discussed, they should be flexible and they should be continuing over a fairly long time. Long-term oversight in this area it seems to me will be necessary.

You might use the analogy—we discussed this at some length earlier this morning—of the problems with clinical trials and the decisions as to how to move from the laboratory to the bedside. In the social sense we need to perform some social trials in this area, I think, before we will clearly see how far we should move in particular applications.

Finally, a few words about the nature of the forum. I have personally for some time favored the establishment of a national, nonregulatory deliberative commission to provide comprehensive overview of our growing potential for intervention in human heredity, and I would now add to that "and development".

Reference has been made to the fact that the advances in the production of external in vitro human fertilization are posing problems somewhat similar in character to that of genetic modification, and that there is likely to be considerable cross-feed between these two areas. That being the case it seems to me that whatever mechanism is now set up, a deliberative commission should look at advances both in heredity and development and their interaction in terms of the problems that they will pose. Such a national commission through expert studies, public hearings, opinions, surveys and so on, could stimulate informed discussion leading to phased recommendations to both the private and public sectors as well as provide liaison with other national and international bodies. And this discussion is going on at least in England and Australia, and in the European Commonwealth.

We are dealing here with a matter that is worldwide in interest. The human gene pool is worldwide, and its custodianship should be a universal human interest and any mechanism we set up it seems to me ought to have open valences, as we say, in connection with similar bodies in other nations or in supranational agencies through continuing oversight and phased recommendation in the commission can accelerate clearly beneficial applications, delay others which cannot be undertaken responsibly and forbid those that offend human sensibilities.

To do these things it will need some kind of linkage with actual policymaking and decisionmaking agencies. As I said before, it seems to me it would be better if it did not itself function in that capacity. We need a defined and open arena to yield accommodative wisdom to guide the new age of potential genetic developmental intervention that clearly lies ahead.

Thank you.

[The prepared statement of Dr. Grobstein follows:]

Testimony presented to the House Sub-committee on Investigations
and Oversight, Committee on Science and Technology, Nov. 18, 1982

Clifford Grobstein
Professor of Biological Science
and Public Policy/UCSD

Mr. Chairman and members of the Sub-committee:

My name is Clifford Grobstein and I am Professor of Biological Science and Public Policy at the University of California, San Diego. I have had long interest in the general area of these hearings, beginning as a laboratory scientist studying mammalian development over several decades, then as Dean of the developing UCSD Medical School and now as an academic analyst of the impacts of advancing genetic and developmental knowledge on the human future.

After the presentations you have heard over the last several days I need hardly reiterate that the subject of this hearing is of profound importance. It is also extremely complex and difficult to fit into conventional policy compartments. For these reasons the initiative taken by your sub-committee is most welcome. Particularly fortunate is the decision to examine the matter in a deliberative setting rather than a confrontational one. After all, as important as the matter is, we do not face an immediate emergency that demands precipitate action. Rather, we probably face an expanding sequence of issues that will evolve over time. What is needed is careful monitoring to anticipate these issues, together with an overall consensus as to strategy in dealing with them. The immediate question, therefore, is the appropriate mechanism for monitoring, continuing deliberation, and consensus development.

Why is it important to begin this process now? First, because controlled and precise intervention in human heredity has been changed in the past decade from fanciful speculation to realistically feasible possibility. Molecular geneticists are isolating, manipulating and even synthesizing genes and inserting them to function in living cells and organisms. Moreover, reproductive biology has opened a window on early human developmental stages via external or *in vitro* fertilization. Comparable early stages in mice have had new genetic information inserted into them and the resulting offspring have been altered in ways that are detectable both in the treated animals and in succeeding generations. Thus, a path is being constructed that could lead not only to human gene therapy but to modified human heredity.

Second, these experimentally established facts have attracted significant public attention and have been portrayed as sources of both possible benefit and threat. The benefit is potential expanded medical capability to deal with at least some of the nearly 3000 identified human genetic defects. The threat is a scenario of extensive genetic modification of human beings to fit malignant purposes of social control and individual exploitation. These are the polar visions of proponents and opponents in the debate over use of genetic knowledge to influence human heredity. The question is thus before us whether in seeking the potential benefit we increase the imagined threat.

Third, the issue arises in a time of controversy and uncertainty about the impacts of other areas of scientific knowledge and their derivative technologies. Most prominently, the fundamental discovery of atomic fission almost a half-century ago spawned military and energy technologies both of which that have aroused great anxiety and controversy. These and other instances have created a climate in which radically new technologies are viewed with suspicion and are as likely to be feared as welcomed. Particularly a technology aimed at the innermost determinants of our individual and collective human qualities raises questions that are too central and unsettling to be easily kept under the rug.

Therefore, I think it not only appropriate but essential that full discussion of this subject should be launched without delay. The fact that this sub-committee has provided a forum for preliminary exploration does not, in my view, mean that federal legislation necessarily is called for or should be regarded as in the offing. It merely signifies that the matter is sufficiently consequential to be considered at the highest levels of national policy-making. It is, in fact, of sufficient consequence to be receiving consideration even supranationally. The Council of Europe has before it a proposal to widen the European Human Rights Convention to take into account possible dangers of human genetic engineering (Nature 295, 545 1982). Thus, both national (in the U.S., Great Britain and Australia) and supranational activities highlight the need for social policy consideration of human genetic and developmental intervention with emphasis on 1) an appropriate forum for deliberation, 2) how an appropriate forum should be constituted, and 3) what should be the initial agenda? These are the three topics on which I should like to comment.

First, what are the characteristics of an appropriate forum for the necessary deliberation? To answer this question one must have at least a preliminary list of the functions to be performed. The following functions appear essential: 1) to bring together the parties at interest; 2) to provide opportunity for presentation of all facts and views by the parties and significant sources of expertise; 3) to appraise carefully the conflicting views of responsible parties and to seek means of accommodation among them; 4) to assure at least informational access to the deliberative process by the general community; and 5) to disseminate as widely as possible the options examined and the rationale for recommended choices.

The list of functions clearly requires a forum of national visibility and of assured credibility, with appropriate staffing for administration,analysis and communication. The charter of the forum should be of long enough duration to allow the specified objectives to be met - a five year interval with the possibility of renewal seems minimal. Precedents for such a forum exist in the two successive Presidential Commissions on Human Experimentation and on Ethical Problems, as well as in the HEW Ethics Advisory Board and the NIH Recombinant DNA Advisory Committee. However, alternatives to a federal forum should also be examined, e.g. a forum organized in the private sector under prestigious university or foundation auspices that might avoid premature commitment to governmental action. Since a private sector forum might lack the authority and relative ease of governmental implementation of recommendations, an intermediate possibility to be considered is a quasi-governmental forum involving appointees by top-level federal officials as well as by relevant professional and public groups.

Although the Commission on Ethical Problems and the Office of Technology Assessment have relevant studies in process neither they nor any other agency exclusively focuses on the area to be examined. Exclusive attention seems important to assure the concentrated and continuing effort that is demanded. This leads to the second question, i.e. how the forum can and should be initiated. The most direct and effective way appears to be through recommendation for Congressional action stemming from these hearings. The very consideration of legislation establishing a suitable deliberative mechanism would extend discussion through hearings and, assuming Congressional approval, would provide the required visibility and credibility. During the legislative process agenda priorities could be established and recorded in the legislative record.

What might such an agenda look like? The following issues seem obvious candidates for inclusion: 1) Does the development of human genetic engineering require any oversight beyond that already in place for human experimentation in general? 2) If it does, should such oversight be applicable to basic human genetic studies that are not specifically aimed at practical uses, e.g. mapping the human genome and establishing the mechanisms by which it operates in normal development? 3) Is special oversight required for genetic modification of human somatic cells? 4) Should there be different oversight for genetic therapy of germinal cells than for somatic cells? 5) Should genetic therapy to correct defects be subject to the same oversight as genetic manipulation intended to improve "normal" hereditary characteristics? 6) Should manipulation to limit genetic capability be subject to the same oversight as therapy to correct defects?

The main objective in formulating and considering such an agenda is to establish a consensus on principles or guidelines to separate sanctioned from non-sanctioned uses of genetic manipulation applied to human beings. The following is intended as a set of examples to illustrate the nature of the principles that might emerge.

1) Genetic manipulation of human somatic cells intended to increase understanding of the nature and function of the human genome in health and disease can be carried out under professional scientific oversight and standards, provided that no individual is placed at undue risk without informed consent.

2) Genetic manipulation of human somatic cells whose purpose is to correct diagnosed genetic defect in order to benefit an afflicted individual should be sanctioned under existing professional medical oversight and standards, including informed consent and approved procedures for clinical trials or for acceptance as established medical practice.

3) Genetic manipulation of human germinal cells whose purpose is to eliminate risk of genetic defects in offspring requires, beyond the medical oversight and standards referred to the second principle, concurrence of a suitably constituted group able to assess probable impacts of such manipulation not only on the lineage directly affected but on the human gene pool.

4) Genetic manipulation of human germinal cells whose purpose is to "improve" genetic characteristics of offspring beyond what may be achieved through normal reproduction should not be sanctioned in the current state of knowledge.

5) Genetic manipulation of human germinal cells that is intended or likely to increase the risk of producing individuals whose hereditary capability is reduced shall never be sanctioned regardless of presumed benefit to society or particular social groups. Suitable means of enjoining such activity should be designed and vigorously implemented.

I repeat that these are samples to illustrate the nature of the guidelines that appear to be needed and are not, either in total content or in the specific wording of a particular guideline, to be regarded as fully considered proposals. Nonetheless some further comment may be in order on the range of issues that are encompassed and that are clearly presented for attention. The first guideline deals with research on the human genome that is independent of formulated or intended practical uses. It asserts that such research should not be limited except by scientific codes of responsibility and considerations of safety. It is intended to minimize limitation of such research and even to encourage it. As such, it might well be opposed by those who fear that greater knowledge of human hereditary mechanisms invades a sacrosanct area and will inevitably lead to unfortunate consequences. It is therefore to be expected that debate over this guideline might modify its language toward greater non-scientific oversight or greater specific restriction. It is also to be expected that with passage of time and greater experience consensus on the language might be modified. It is this policy-making process that a suitable forum would facilitate.

Similarly, the second guideline is phrased to sanction genetic therapy of somatic cells that falls withn existing procedures for medical practice. It implicitly assumes that genetic engineering in this context is no different in principle or consequence from a pharmacological or surgical intervention and should be carried out under similar forms of oversight. It might be opposed by some on the ground that its successful use will necessarily bring us a step closer to capability for modification of germinal cells and applications that escape the bounds of the medical model. The concern is addressed in the remaining three principles which place successively greater strictures on several conceivable uses of genetic modification of human germinal cells.

It should be noted that the strictures mentioned require mechanisms of implementation that go beyond what is currently available. Thus, the third principle addresses genetic therapy effective over generations and calls for overview by a group constituted to provide assessment of effects on the human gene pool. This group would be analogous to current institutional review boards (IRB) that examine ethical considerations and the function might, in fact, be linked to such boards. It is important to note,however, that the problems faced by current IRB's require overlapping but not identical expertise and that, therefore, simple assignment of the responsibility to the existing IRB's should be carefully evaluated.

The fourth principle places at least temporary stricture on so-called eugenic use of genetic engineering. One basic argument for the restriction stems from the current rudimentary state of our knowledge of both the organization and the function of the human genome. Intense research activity of the past five years, taking advantage of the rapidly expanding technology of genetic engineering, has been spectacularly successful in opening new prospects for greater knowledge but also in demonstrating great genomic complexity that is only beginning to be fathomed. It is already clear that while new genetic information can be introduced into complex genomes it is not at all certain what the consequences would be, especially in terms of the genetic complexity of many human characteristics that are frequently mentioned as candidates for improvement.

The fourth principle, therefore, would put a moratorium on any efforts in this direction. The principle makes no reference to how such a moratorium would be declared or implemented - a matter that will be returned to shortly. The fifth principle defines a forbidden use - genetic engineering to limit or reduce the hereditary capability of human beings for any purpose. There is not at the moment any rationale or capability for attempting such limitation. It does, however, represent a frequently expressed anxiety in considering any form of human genetic engineering. It would clear the air significantly if this anxiety were set to rest by national, and even international law.

The set of sample principles therefore can be thought of as a spectrum in terms of levels and mechanisms of oversight that may be desirable. It also emphasizes that a premature effort at legislative solution could vastly over-simplify the problem and sacrifice important benefits to excessive and unrealistic anxiety. We face issues that will not be successfully resolved in a week, a year, or even a decade. I believe that appropriate oversight is needed but that it must be carefully tailored in nature and degree to particular issues as they become clear and imminent. We will gain nothing by seeking to confine shadows.

A necessary first step is to establish a focus for monitoring, anticipating, analyzing and debating appropriate cases and courses. I have favored for some time- as voiced in the early stages of the recombinant DNA debate (Science 194:1133-35 1976)-the establishment of a deliberative commission charged to maintain a comprehensive overview of emerging powers for human genetic intervention. With the advent of external human fertilization and its readily imagined convergence with genetic engineering I have broadened the suggestion to the establishment of a deliberative, non-regulatory national commission on intervention in human heredity and development. The Commission should be empowered to support expert studies, to hold public hearings, to conduct surveys, to publish findings and, in all feasible ways, to stimulate discussion and understanding.

Such a commission would fulfill the requirements outlined earlier for a discussion forum. From its deliberations should come phased recommendations for appropriate actions by private organizations and public agencies, thereby acting to coordinate public and private sectors in essential cooperation. Such a national commission could also maintain liaison with comparable groups in other countries. For, in the long run, the problems being discussed are not limited to particular nations. The human gene pool is world-wide and its custodianship is a concern and responsibility of all of humanity.

I believe that a commission such as I have described is an appropriate and essential policy response to the current status of interventive genetic and developmental capability in the human species. It can accelerate research leading to the realization of medical benefits where these depart very little from traditional modes of therapy. It can put "on hold" other applications with respect to which our knowledge is not yet adequate to proceed responsibly. And it can draw firm lines beyond which applications may not ever go because they offend our deepest sense of humanity. In the process there will be conflict and controversy. But, hopefully, out of conflict and controversy in a defined and open arena can come accommodative wisdom to guide the new age of genetic and developmental intervention that clearly lies ahead.

Mr. GORE. Prof. Patricia King, from Georgetown University.

Ms. KING. I should also say in addition to being a professor of law at Georgetown University I have in the past served as a member of the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Rresearch, a member of the Recombinant DNA Advisory Committee, and briefly as a member of the President's Commission on Ethics. I believe I am the only person to have served on the three commissions that have responded in the past to problems of science.

Mr. GORE. We are all ears.

Ms. KING. I would be very happy to answer questions about the different models. I just thought I should state the above at the outset before proposing models here.

My name is Patricia King. I am an associate professor of law, Georgetown University Law Center. I appreciate the opportunity to testify before you concerning social policy issues associated with human genetic engineering.

Let me state at the outset two assumptions that underlie my testimony. First, while human genetic engineering is likely to be with us in the near future, to my knowledge, it has not yet been successfully accomplished with humans.

We are, therefore, not completely informed with respect to all implications of its use.

Second, since the phrase "genetic engineering" has been used in different ways, perhaps I should begin by making explicit the way in which I use it here. The new college edition of the American Heritage Dictionary defines engineering as the application of scientific principles to practical ends as the design, construction and operation of efficient and economical structures, equipment and systems.

It seems to me that the essence of the definition is the notion of design and construct. As applied to genetics, the word "engineering" would, therefore, appear to describe the creation and design, including transmission, expression, or effects, of genes.

Specifically, I have in mind the use of the techniques of modern molecular biology to add genetically determined characteristics to cells that would not otherwise have them.

Since I am discussing human genetic engineering, I have in mind, of course, adding genetically determined characteristics to human cells.

My use of the phrase "human genetic engineering" would, therefore, exclude engineering of nonhuman cells and reproductive technologies such as artificial insemination by donors—AID—that potentially affect the occurrence of genes in the population but do not require alteration of the structure of the cell, itself.

While I exclude certain reproductive technologies from my use of the phrase, I wish to make clear that human genetic engineering techniques are capable potentially of modifying both the reproductive—germ—cells as well as other—somatic—cells. By altering germ cells, however, the modification would be carried forth to successive generations.

Modifications of both germ and somatic cells would require replacing single bad or defective genes with good or normally functioning genes. The precise techniques for modifying genes of somatic cells undoubtedly would differ from techniques for modifying germ cells. The latter modifications would probably involve in vitro fertilization and modification of embryonic cells, while the former might take place at any point in human development.

The prospect of replacing defective genes with normally functioning genes offers hope that we may be able to cure or prevent some genetic diseases caused by single genes. At the same time, there is the possibility of misuse of these techniques because we may attempt to structure or design our offspring.

We are rightly concerned about the latter possibility because we are all too aware of past attempts to affect the human gene pool.

We are mindful not only of eugenic policies carried out in Nazi Germany, but can anyone forget the growth and widespread acceptance of the eugenics movement in this country, especially in the first half of this century?

During that period we sterilized mentally handicapped persons because we believed that we could reduce the incidence of mental disability in the population.

The infamous words of Mr. Justice Holmes have continued to resound down through the decades. In holding in *Buck* v. *Bell* that it was constitutional for Virginia to sterilize Carrie Buck as long as it was done in accordance with due process of law, he said, by way of justification, "three generations of imbeciles are enough."

Fortunately, the Supreme Court had a somewhat different reaction in *Skinner* v. *Oklahoma* where Mr. Justice Douglas, in striking down an Oklahoma statute permitting sterilization after a third conviction for a felony involving moral turpitude but excluding such felonies as embezzlement, stated, "we are dealing here with legislation which involves one of the basic civil rights of man. Marriage and procreation are fundamental to the very existence and survival of the race." However, we should remember that *Buck* v. *Bell* has never been overruled, and currently 21 States have statutes that permit sterilization of certain persons.

Moreover, we must be cognizant of the subtle consequences of permitting prenatal diagnostic techniques with the possibility of abortion of affected fetuses or sperm banks stocked only with the sperm of Nobel Prize winners and other distinguished scientists and mathematicians.

It seems to me that these and other techniques subtly foster the idea that offspring with certain characteristics are preferred to others. Let me hasten to add that I am not necessarily disapproving of the use of these techniques. However, as with so many things, they may have adverse as well as beneficial effects.

Alteration of the occurrence of genes in the population traditionally has been a slow, highly inefficient, and ad hoc process. The new techniques of molecular biology offer the prospect of rapid and efficient changes in the genetic fabric of society. They, therefore, present us with challenges that have new dimensions.

They will not only permit the reduction of the incidence of genes which cause untold human pain and suffering, but, for the first time, will allow the design and structuring of genetic characteristics.

Against a historical tradition that has accepted the inferiority of some persons because of race, sex, national origin, religion, or handicap, this potential to affect the genetic fabric of society is awesome, indeed.

Our challenge then comes down to determining what, if any, consequences of human genetic engineering are desirable and beneficial, while, at the same time, avoiding consequences that have been determined to be undesirable.

It is a twofold challenge. We must determine what are desirable and undesirable uses of the technologies, and we must next devise a structure or mechanism of some sort that offers the reasonable prospect of reducing undesirable uses and consequences.

Keeping in mind that first, these techniques are not now appropriate for use with humans; second, that full implications of their use are not known; and third, public concern and opinion have not yet jelled with respect to these potential techniques, I would suggest that the immediate social issues are not whether development of these techniques should be banned or whether comprehensive Federal regulation is warranted.

Instead, I suggest that the immediate social issues involve: One, fostering continued public debate of the prospects of these techniques utilizing accurate information about these techniques and avoiding terrifying and obfuscating slogans, and two, developing oversight and monitoring mechanisms which keep track of scientific developments and possibly provide interim substantive guidance as appropriate.

In responding to the immediate social issues, I would urge that a ban on the development and use of technologies to achieve human genetic engineering would be a grievous mistake. First, human genetic engineering offers the promise of benefit as well as the potential for abuse.

I am confident that minimally there would be a consensus in this society for avoiding the pain and suffering associated with sickle-cell disease or beta thalassemia. A ban seems to me to be undesirable and a disproportionate response to our fears of abuse if great benefits are also possible. If we fear abuse, the more logical approach would be to proceed cautiously and to devote time and energy to newer and more effective methods of control.

Some would assert that to intentionally modify natural human processes is, in effect, to play God. My response would be that we have already interfered with natural processes.

Clearly, artificial organs, organ transplants, artificial insemination and prolongation of life—or dying—challenge traditional notions of what we mean by life, death, and humanness.

I have not been able to discern a relevant difference between these accepted treatments and procedures, on the one hand, and designed genetic change, on the other. To be sure, there are differences but only of degree.

Still others assert that our society does not have the wisdom to handle the implications of new knowledge once obtained. I believe this to be a variation of the we should not play God argument. However, I am firmly of the view that decisions will be thrust upon us in any event, and that we should face up to, not duck, our awesome responsibilities.

A second consideration that suggests that a ban is an inappropriate response is that another significant value in our society, freedom of scientific inquiry, is at issue. While I do not accept the notion that this freedom is absolute and not subject to regulation, I do urge that bans and extensive regulation be regarded as drastic measures subject to heavy burdens of proof as to their necessity.

Finally, a ban would not be easily enforced especially if there are widespread views that the techniques offer the prospect of benefit. Much research is done abroad, and beyond our control, in any event.

Moreover, since no unique or controllable materials are needed in this research, there are likely to be a number of research sites, many of which would be able to exist underground. At most, therefore, we would slow down but not halt this research.

I also urge that comprehensive regulation enforceable by an existing or newly created agency would seem premature at this time, although it may be warranted in the future. It seems to me that effective agency regulation presupposes that basic value issues are not in conflict and that congressional intent is reasonably clear.

Neither presupposition would obtain here. Moreover, it would be difficult to establish a broad regulatory scheme where genetic engineering techniques and their implications are not completely known. I suggest we need experience before we codify broad standards. To do otherwise risks losing flexibility, open debate and broad social participation.

At present, no Government agency or commission has exclusive oversight responsibility or control over human genetic engineering, although many agencies or departments have oversight or control over aspects of the process. Among these are HHS through the National Institutes of Health, which has authority over human subjects research and recombinant DNA research.

However, this authority does not extend to privately funded research, although the recombinant DNA guidelines have permitted and encouraged review of industry protocols on a volunteer basis. Moreover, the recombinant DNA guidelines have focused on issues of safety and not the social and ethical implications of the research. This is also true of other agencies that are involved with genetic engineering where focus has been on hazards to workers, environment, or commercial aspects.

However, it should be possible to use the procedure of biohazard committee review to keep NIH informed of developments with identified recombinant DNA techniques. I am not suggesting that these protocols be reviewed by the Recombinant DNA Advisory Committee—RAC—unless review is required by existing guidelines.

However, with appropriate funding, it should be relatively easy to set up a data-gathering apparatus, making use of existing structures. In this manner, we could continue to track the development of techniques that will permit human genetic engineering.

Any human genetic engineering attempts that are the result of Government funding would presently require review by an institutional review board—IRB—applying existing regulations on human subjects research. Although federally funded research on fetuses is covered by existing regulations, the current definition of fetus at 46 CFR 46 is as follows: 46.203(c) " 'fetus' means the product of conception from the time of implantation * * * until a determination is made, following expulsion or extraction of the fetus, that it is viable."

This definition excludes research on the developing human entity prior to implantation and therefore does not cover in vitro fertilization.

Current regulations state that:

> No application or proposal involving human in vitro fertilization may be funded by the Department * * * until the application or proposal has been reviewed by the Ethical Advisory Board and the board has rendered advice as to its acceptability from an ethical standpoint.

The issues of in vitro fertilization were considered by an Ethics Advisory Board—EAB—which submitted its report and conclusions on May 4, 1979. Among its conclusions was the following.

Conclusion No. 2. The Ethics Advisory Board finds that it is acceptable from an ethical standpoint to undertake research involving human in vitro fertilization and embryo transfer provided that:

> A. If the research involves human in vitro fertilization without embryo transfer, the following conditions are satisfied:
>
> 1. The research complies with all appropriate provisions of the regulations governing research with human subjects (45 CFR 46);
>
> 2. The research is designed primarily: (a) to establish the safety and efficacy of embryo transfer and (b) to obtain important scientific information toward that end not reasonably attainable by other means;
>
> 3. Human gametes used in such research will be obtained exclusively from persons who have been informed of the nature and purpose of the research in which such materials will be used and have specifically consented to such use;
>
> 4. No embryos will be sustained in vitro beyond the stage normally associated with the completion of implantation (14 days after fertilization); and
>
> 5. All interested parties and the general public will be advised if evidence begins to show that the procedure entails risks of abnormal offspring higher than those associated with natural human reproduction.
>
> B. In addition, if the research involves embryo transfer following human in vitro fertilization, embryo transfer will be attempted only with gametes obtained from lawfully married couples.

The report and conclusions were, unfortunately, never adopted by HEW—now HHS. Moreover, the EAB no longer exists.

It seems to me that we could meet our immediate goals of fostering public debate and monitoring scientific developments through utilization, with some modification, of existing structures such as the Institutional Review Board [IRB] and the Institutional Biohazard Committee [IBC]; adoption of earlier EAB recommendations; and reactivation of the EAB.

Although I would prefer to see the continued operation of the President's Commission on Ethics, that option is apparently foreclosed, and I recommend reactivation of the EAB as an acceptable but less desirable alternative.

We could provide for monitoring scientific developments by requiring that information with respect to identified categories of research be passed from IRB's and IBNC's to a central office such as an administrative structure which supports a reactivated EAB.

Adoption of the report and conclusions of the EAB dated May 4, 1979, would establish a policy governing in vitro fertilization, including the case where implantation of the fertilized ovum is not contemplated.

Reactivation of the EAB would establish an interim structure in HHS that would be designed and charged with considering the ethical and social issues in human genetic engineering. This board's composition should be similar to that of the earlier EAB and obviously would have representation of outstanding scientists, ethicists and lay persons and adequate funding to carry out its functions.

Mr. GORE. Let me interject, Dr. King, that I hope your assessment of the likelihood of congressional action is wrong, and I do believe that there is sufficient agreement from all points of the ideological spectrum with very few exceptions on the need for an oversight body of the kind that various witnesses have described and assigned characteristics to.

I think there is wide agreement on that, and, as a result, it may be easier than normal to get something through the Congress, and I would anticipate some action in the new Congress on that.

Ms. KING. Congressman, all I can say is, I hope you are right, so that everything I am saying here will not be necessary.

I do hope that is the case, and I do not mean to sound unduly pessimistic. It has just been my experience that sometimes these matters proceed slower than we would like, but if I am wrong, I will be happy.

Mr. GORE. Which is not to say that your discussion of the existing mechanisms would be mooted, not at all, because even if we are successful in establishing this oversight body, one of the important questions remaining would be its relation to the existing mechanisms.

You mentioned the information flow problem or opportunity, and there are many others. So, excuse me for interrupting. Go ahead.

Ms. KING. It would appear that reactivation of the EAB has two major weaknesses. First, the EAB is an advisory arm of the Secretary of HHS and, as such, would not necessarily enjoy maximum independence from political and budgetary constraints operating on the department. Second, the EAB would be concerned only with Government-funded research.

I certainly concede that the first point is a major weakness. I would certainly prefer to see a national commission or a Presidential commission to oversee this area. They have traditionally functioned independently of such constraints and as a result have exercised great influence over developments in the scientific and medical establishments.

However, I understand that Congress has declined to date to extend the life of the President's Commission on Ethics.

An ethical advisory board, while a less desirable alternative, is an acceptable one, especially if great care is taken to select diverse and truly outstanding members. I also emphasize that its establishment is only regarded as an interim measure.

Any proposal that does not contemplate regulation of the private sector would necessarily be limited to Government-funded research. This is a particular problem with human genetic engineering, because much of the development of scientific techniques is in the hands of private concerns.

However, for an interim period, perhaps voluntary cooperation would work. This has been the case with respect to recombinant DNA research, and as far as we know, there have been no violations of the guidelines. Voluntary cooperation is not an ideal solution, but for reasons stated previously I believe that comprehensive Federal regulation at this time is premature.

In conclusion, I urge that the ethical and social issues raised by human genetic engineering are quite serious ones with far-reaching implications for our society. While I am aware that the rapidity of scientific discoveries have often outstripped society's ability to provide standards by which to evaluate these advancements, I would nevertheless urge a course for the near future that maximizes use of existing structures while we continue to publicly debate and evaluate the implications and possible limitations of human genetic engineering.

I will close here.

Mr. GORE. Thank you very much.

Prof. Stephen Stich.

Mr. STICH. Thank you, Mr. Chairman.

I am pleased to be here. With your permission, Mr. Chairman, I will skip over some of the preliminary parts of my testimony and go right to the core of the prepared statement which focuses on a rather long-term perspective on the issue. I take that perspective for two reasons: first, I am by profession a philosopher and we tend to think of things in terms of generations and centuries, a rather different time scale perhaps than political leaders do. But, much more practically, I am struck by the remarks of a number of good scientific friends who are my advisers in thinking about these matters. Each time I have discussed this with them over the last 2 or 3 years they have said the same thing which is that every time they have attempted to estimate how quickly a particular technical innovation would arise in the field of genetic engineering, they have underestimated. I became particularly concerned about this when one scientific friend said that his batting average was so bad that he was tending to underestimate by an order of magnitude, that is to say, he was getting it 10 times too long.

The testimony presented before this committee during the last 3 days has made one thing abundantly clear. Humankind is embarked on an extraordinary adventure, an adventure promising rewards that could barely have been imagined as recently as a generation ago. But that adventure poses moral and social dilemmas every bit as daunting as the rewards are enticing. Moreover, some of those dilemmas are so unique, so utterly unprecedented in human history that the tradition of Western moral philosophy has left us quite unprepared to deal with them. Within the moral and conceptual frameworks bequeathed to us by our cultural tradition, we hardly know how to begin thinking about some of the deeper problems posed by human genetic engineering. A central theme of my testimony today will be that we had best start learning how to think about these problems and soon.

We have already seen the first tentative—some would say premature—applications of recombinant DNA technology to humans. These efforts have been in the domain of so-called somatic therapy, aimed at correcting a genetic defect in cells or organs which are not involved in reproduction. If successful, somatic therapy will alleviate the illness of the patient who receives the therapy, though he will still be a genetic carrier of the disease, and will run the risk of passing his defective gene or genes on to his offspring. There are many vexing questions about the proper regulation of research on new somatic therapies. But, by and large, these issues are variations on a familiar theme—the use of human subjects in medical research. I am inclined to think that the existing system for regulating and reviewing research involving human subjects can be extended to research on somatic therapies with little difficulty. Thus I will have nothing further to say about somatic therapy in these remarks.

A considerably more vexing cluster of problems arise when our attention turns to therapeutic procedures which involve the reproductive process. Typically, such procedures will be aimed at subsequent generations, with the goal being to prevent a defective gene from being passed on from parent to child. As genetic therapy of this sort progresses, there is reason to hope that such scourges as Tay-Sachs disease, Huntington's Chorea and sickle cell disease will be all but wiped off the face of the Earth. However, research in this domain will inevitably involve not only human sex cells but also human embryos and fetuses. Neither ethicists nor the society at large has reached any consensus about the moral propriety of such research or the rules under which it should be conducted. If we aim at a consistent, coherent set of moral principles, then there will be no separating the regulation of gene therapy research from the ongoing controversy over the morality of abortion, for in both cases the central issue to be confronted is the moral status of the human embryo. I am, by profession, a teacher of philosophy, and in my courses I often find myself lecturing on this issue. There is, I confess, a strong temptation to repeat some of those lectures here, but I will forbear. For I think there are even deeper difficulties to be confronted as work in human genetic engineering progresses, and it is to those issues that I will devote the remainder of the time available to me today.

To focus in on the issues I have in mind, let us speculate on the possible future of research in genetic engineering. It seems clear that in the decades ahead research yielding knowledge relevant to human genetic engineering will continue and accelerate. Much of the research which expands our knowledge about the mechanisms of genetics will not involve human subjects, though inevitably as this basic knowledge is applied there will be increasing use of human subjects in genetic engineering studies both in this country and abroad. I think these developments are inevitable because there are powerful social and economic motives to pursue genetic engineering research on a broad front. What is more, I think the acceleration of research in this area is to be welcomed. The medical, industrial and agricultural applications of genetic engineering research will transform our society in ways even more profound than the computer revolution now well underway. And I am enough of an optimist to believe that most of these changes will be for the good. However, as we learn more about the mechanisms of human genetics, it is also inevitable that we will start learning how to manipulate the human genome to suit our tastes, or what we perceive to be our needs, in domains far removed from those that have traditionally been the concern of medicine.

At first this ability will be restricted to characteristics under the control of a single gene or a small number of genes. But, as our knowledge progresses, we will learn more and more about how to manipulate those characteristics of human beings—both physical and mental—which are under the control of many separate genes. In our current state of knowledge, we simply do not know the extent to which aspects of intelligence and personality are under genetic control and thus susceptible to genetic manipulation. But, as I read the evidence we now have, there is every reason to think that a substantial component of our mental and moral lives is influenced by our genetic endowment. In saying this, I do not mean to endorse a simplistic biological determinism. Obviously, our environment and our childhood experiences play a substantial role in determining what we accomplish in our lives. But it is equally obvious that all people are not endowed with equal potential, either physically or mentally. I am 5 feet 9 inches and have a tenor voice which, my 6-year-old daughter insists, sounds like a cat howling in the night. Nature simply did not endow me to pursue a career as an opera singer or a professional basketball player. It would be remarkable, indeed, if we did not all come genetically equipped with mental strengths and weaknesses more or less analogous to our innate physical strengths and limitations.

As our ability to manipulate the genetic composition of our own offspring grows in sophistication in the decades ahead, the social pressures to use this new technology will become intense. During the last year or two we have seen an explosion of interest in home microcomputers; many of the people who buy these wonderful, expensive, machines do so in the hope that they will give their children a competitive edge in a technologically competitive world. Closer to the fringes of our society we have seen that some women are prepared to have themselves impregnated with the sperm of a Nobel Prize winner in the hope of bearing an intellectually gifted child. Both of these phenomena underscore the fact that the desire to help one's children to excel is a powerful and widespread motivational force in our society. When, via genetic engineering, we learn how to increase intelligence, memory, longevity, or other traits conveying a competitive advantage, it is clear that there will be no shortage of customers ready to take their place in line. Moreover, those who are unwilling or unable to take advantage of the new technology may find that their offspring have been condemned to a sort of second class citizenship in a world where what had been within the range of the normal gradually slips into the domain of the subnormal.

Now obviously if history unfolds more or less along the lines that I have been predicting, there will be no shortage of social problems generated. Insuring equitable access to the new technology and protecting the rights of parents and children who have chosen not to utilize the technology are two which come quickly to mind. These issues, however, are once again variations on a familiar theme. We already have analogous problems with equal access high quality education for children. And in the decades ahead we will increasingly have to worry about the technological illiteracy of people from deprived educational backgrounds. I do not mean to suggest that these are unimportant concerns; far from it. Still, I am inclined to think that if problems of equity and discrimination were the only problems it generated, most people would welcome human genetic engineering as an almost unmixed blessing. Given the enormous increase in knowledge required to function in our increasingly technological society, it might well be argued that the capacity to improve our learning and reasoning abilities by genetic engineering had arrived just in the nick of time.

As we gradually map and learn to manipulate the human genome, however, it will become possible to alter or enhance many traits, not merely those, like intelligence and memory capacity, which are generally desirable and convey an obvious competitive advantage. We already know that many physical characteristics—height, build, color of the hair, eyes and skin, for example—are in part determined by our genetic endowment. It is a good bet that tastes, character traits and other aspects of personality have a substantial genetic component as well. I do not think it is beyond the bounds of realistic possibility that in the next generation or two, and perhaps very much sooner, prospective parents will be able to choose from a library of genes in redesigning their own offspring. Nor is there any reason to suppose that all people or all societies will make the same choices. However, if different societies, or different groups within our own society make systematically different choices for several generations, we may begin to see the genetic fragmentation of the human species. The divisions that separate cultural groups may come to include genetic differences so profound that members of different groups will no longer be interfertile.

I said earlier that the western tradition of moral philosophy has left us unprepared to deal with the dilemmas posed by genetic engineering. I would like now to spend a few moments expanding on that theme. Consider first the quandaries that arise when we try to think about such central ethical questions as the nature of the good or moral life, against the background of the emerging genetic engineering technology. From Socrates down to the present, just about everyone who has pondered the question of how men and women ought to live their lives has presupposed that human nature is in large measure fixed. There have, of course, been profound disagreements about what human nature is like. However, the moral issue has always been conceived of as attempting to determine what sort of life a person should lead, given that a human being is a certain sort of creature. This tradition leaves us radically unprepared to think about the questions forced upon us by the prospect of human genetic engineering. Sometime within the next century, and perhaps much sooner than that, the age old presumption of a more or less fixed human nature may begin to dissolve. It will no longer suffice to decide what constitutes the good or moral life for the sort of creature we happen to be; we shall also have to decide what sort of creature—or creatures—humankind ought to become. The options that human genetic engineering will make available are impossible to foresee in detail, though there is every reason to suspect that they will be numerous. No previous generation has had to give serious thought to such choices. Thus the moral and conceptual tools required to think about them will have to be invented as we go along.

A worry of a rather different sort arises when we turn our attention to the processes of moral dialog and the attempt to resolve ethical disputes. In the western philosophical tradition there are many views about the nature of rational moral dialog and the quest for ethical agreement. But there is, I think, a common strand that runs through just about all theories on this subject. In one way or another, the notion of a shared human nature is rung in to explain how it is possible for people to reach a meeting of the minds on moral matters. When we are able to transcend our cultural and ideological differences, and agree on some ethical principle or judgment, it is because, despite our manifest differences, we share our humanity in common. Of course, our commonalities are all too often overwhelmed by our differences, and when this happens reason and dialog may give way to force. But at least our common nature gives us reason to hope that we share some common ground on which our attempts at rational persuasion can be built. However, human genetic engineering threatens to undermine the foundations of rational ethical dialog by fragmenting our common nature along social and ideological lines. How shall I reason with a Moslem fundamentalist or a Marxist or a Moonie if what divides him from me is not merely his traditions and his convictions, but also his genetics? The prospect is at once so staggering and so unprecedented that we hardly know how to begin thinking about it.

Plainly there will be difficult decisions down the road if genetic engineering technology proceeds as I have been supposing it will. On looking ahead to the problems that genetic engineering will likely raise, many people are inclined to think that the proper course of action is to put on the brakes in an effort to avoid ever reaching the point where these hard choices will have to be made. Many find it deeply distressing that we should even contemplate significant alterations in the human genome. Others worry that the power to quite literally remake our species is a power that humankind will not use wisely, and because of this worry they urge that we take steps now to insure that this power will not be acquired. I have considerable sympathy with some of the concerns that underlie the recommendation to put on the brakes, though that is not the recommendation I would make. Let me sketch very briefly what I take to be the core of the disagreement between myself and those who hope we shall never acquire the ability to alter the human genome in a significant way.

There are, I think, two rather different arguments that have led people to think that we ought not to acquire the capacity to manipulate the human genome. One of these arguments is theological. God, it is said, designed man as He wished man to be, and man alters God's plan at his peril. Now, I am no theologian, but it seems to me that this is an argument which should evoke deep skepticism. For, even if we grant for the sake of argument, that God has a design or plan for the human species, we must take account of the overwhelming weight of the evidence indicating that He chose to unfold this plan via the mechanisms of evolution and natural selection. Species are not fixed over time, and each of us alive today had distant ancestors who were far more genetically different from us than we are likely to be from any imaginable genetically engineered descendants. The fallacy of the theological argument is to equate the divine plan with the status quo. Since the Renaissance, this sort of argument has been used repeatedly in an effort to oppose technological or social innovations which threatened to have a major impact on the structure of societies and the way people live their lives. None of us, I would venture, is tempted to think that the technological, social, and economic patterns of the late Middle Ages reflected God's plan for how we should live our lives. Nor do we think that there is anything sacrosanct about the genetic endowment of our Cro-Magnon forebears. I see no more reason to think that God's ultimate genetic plan—if He has one—is reflected in the genetic composition of late 20th century humankind.

The second argument again acquiring the capacity to manipulate the human genome rests not on a theological premise, but on a scientific one. The current constitution of the human gene pool, it is argued, is no accident. We got to be the sort of creatures we are as the result of millions of years of natural selection. During those millions of years, many genes disappeared from the gene pool because the characteristics they impart to the organism were less adaptive than the surviving alternatives. Thus there is a sense in which the current genetic makeup of humankind stores a great treasury of information about the sort of design that can flourish in our environment. It is folly, this argument concludes, to fiddle with the hard-won evolutionary wisdom that has been bequeathed to us in our gene pool. Since we are dealing with such a complex and well-adapted system, any modification we make is likely to do more harm than good. And if modifications come to be made for capricious reasons, the results may well be disastrous.

Now, although I ultimately disagree with this argument, I have considerable sympathy with the central insight it is urging. Human beings—indeed, all currently existing species—are highly evolved, extraordinarily complex, and marvelously well adapted to their natural ecology. We should be very wary indeed about altering components of this system until we have a good understanding of what role the components play in the overall organization of the system. However, it is one thing to suggest that we act cautiously, keeping in mind the fact that there are generally good evolutionary reasons for an organism's genome being the way it is. It is quite another thing to suppose that natural selection cannot be improved upon. To accept that view is to accept the Panglossian assumption that the status quo is the best of all possible worlds and that assumption is simply not true. A single example may serve to make the point. It now appears that the gene for sickle cell disease survived and flourished because an individual who carries only one such gene is better able to cope with malaria. In an area where malaria is endemic, the sickle cell gene conveys a selective advantage. However, when the swamps are drained and the mosquito population declines, the sickle cell gene is no longer worth having. What this example illustrates is that genes which may have been useful in the environment in which the species evolved may cease to be adaptive when the species finds itself in a new environment. But, of course, the environment in which humankind now exists is radically different from the environment which shaped the genome of our hunter-gatherer forebears. Thus there is every reason to think that the results of natural selection can be improved on. Indeed, to repeat a theme I sounded earlier, it may well be that our social environment is changing so rapidly that the technology allowing us to modify our own genome will prove to have arrived just in the nick of time.

Let me close with some brief observations on the policy implications of these reflections. As I have already indicated, I think it would be a serious mistake to adopt policies aimed at preventing the development of a technology capable of making major modifications in the human genome. However, it is certainly an area that cries out for ongoing, informed monitoring. Thus I endorse with enthusiasm Professor Capron's proposal for an independent body, made up of scientists, ethicists, religious leaders, educators, and lay people whose function would not be to regulate, but to study issues as they appear on the horizon. Professor Capron stressed that education would be an important function of this body, and with this I also agree. However, I am inclined to urge a much stronger role for education in dealing with the challenge of genetic engineering and other new technologies. Unless the public and the political leaders who represent them come to have a better understanding of the basic science underlying these new technologies, there is little hope that our social decisions will be wise ones. This understanding does not come easy, and it will be expensive, but in the long run the distressingly low level of scientific understanding in our society will be more expensive still.

Mr. GORE. Thank you, Doctor, very much.

Our final witness on this panel and our final witness of today and the 3 days is Dr. Bernard Talbot, Deputy Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md.

We welcome you and invite you to proceed.

Dr. TALBOT. Thank you.

I am here today, Mr. Chairman, in response to your letter of November 10 to NIH Director James Wyngaarden, requesting that NIH send a staff member to testify who is familiar with the case of Dr. Martin J. Cline.

I served as executive secretary of a committee of NIH staff appointed by former NIH Director Donald Fredrickson in October 1980 to look into certain research activities of Dr. Cline. Our final report was accepted by Dr. Fredrickson, and made public in May 1981. Our findings may be summarized as follows:

In May 1979, Dr. Cline, professor of medical oncology at the University of California, Los Angeles, and collaborators submitted a protocol for review to the UCLA Human Subject Protection Committee which proposed the insertion of recombinant DNA into human subjects.

Following extensive discussions between Dr. Cline and the UCLA committee, including revision of the protocol by Dr. Cline, and written comments on the protocol solicited by the UCLA committee from four outside consultants, all of whom responded that more animal studies should be done prior to the proposed human experimentation, the UCLA committee voted on July 16, 1980, to disapprove the protocol.

Prior to the UCLA committee disapproval, on July 10 and July 15, 1980, Dr. Cline inserted recombinant DNA into a patient in Israel and a patient in Italy. He had prior approval of the Israeli human subject protection committee to insert DNA, but not recombinant DNA, into the patient.

The UCLA Human Subjects Policy Committee concluded that Dr. Cline's activities in Israel and Italy were not in conformance with requirements for UCLA scientists to have approval of the UCLA committee for their human subjects research even if conducted at a foreign site. The UCLA Institutional Biosafety Committee concluded that Dr. Cline's injection of recombinant DNA into humans was in violation of the NIH Guidelines for Recombinant DNA Research.

Dr. Cline wrote on January 16, 1981,

> I greatly regret my decision to proceed with the use of recombinant molecules without first obtaining permission from the appropriate committees. I exercised poor judgment in failing to halt the study and seek appropriate approval . . . I profoundly regret that I conducted these studies without adhering strictly to written guidelines.

While our NIH committee was assembling the facts in this case, UCLA also was investigating. The UCLA investigation was concluded with the acceptance of Dr. Cline's resignation as Chief of the Division of Hematology-oncology of the Department of Medicine.

Dr. Cline's letter of February 25, 1981, formally submitting his resignation as Division Chief, stated,

> My reasons for resigning relate to circumstances surrounding clinical trials of gene therapy conducted in Israel and in Italy in July of 1980. I included recombinant DNA molecules in the preparations used to introduce new beta-globin genes into the patient's bone marrow without expressly requesting to do so from the Israeli Recombinant DNA Committee."

Dr. Sherman Mellinkoff, dean of the UCLA School of Medicine, in his reply on February 26, 1981, accepting Dr. Cline's resignation as Division Chief, wrote,

> An entirely new and unprecedented experiment was knowingly used in two patients without the approval of the appropriate UCLA and Israeli committees to conduct the experiments actually performed.

Dr. Cline's resignation as Division Chief included termination of other responsibilities associated with that position, including director of the medical oncology program of the Jonsson Comprehensive Cancer Center.

Mr. Gore. Dr. Talbot, if you will forgive me, I am going to make the recommendation that we put the rest of your prepared statement in the record.

We had originally hoped to have something of an official NIH statement on the larger issues as well.

I understand the reluctance of NIH to take an official position and what was worked out was that you were going to testify, but I see now that it is a very extensive treatment of the NIH's response and I think it would be more appropriate to have that included in the record at this point. Is that OK with you?

Dr. Talbot. Fine.

[The prepared statement of Mr. Talbot follows:]

Testimony of Bernard Talbot, M.D., Ph.D.,

To be Given November 18, 1982,

Before the Subcommittee on Investigations and Oversight,

Committee on Science and Technology,

U.S. House of Representatives

I am Dr. Bernard Talbot, Deputy Director of the National Institute of Allergy and Infectious Diseases at the National Institutes of Health (NIH). I am here today, Mr. Chairman, in response to your letter of November 10 to NIH Director James Wyngaarden, requesting that NIH send a staff member to testify who is "familiar with the case of Dr. Martin J. Cline."

I served as executive secretary of a committee of NIH staff appointed by former NIH Director Donald Fredrickson in October 1980 to look into certain research activities of Dr. Cline. Our final report was accepted by Dr. Fredrickson, and made public, in May 1981. Our findings may be summarized as follows:

In May 1979, Dr. Cline, Professor of Medical Oncology at the University of California, Los Angeles (UCLA), and collaborators submitted a protocol for review to the UCLA Human Subject Protection Committee which proposed the insertion of recombinant DNA into human subjects. Following extensive discussions between Dr. Cline and the UCLA Committee, including revision of the protocol by Dr. Cline, and written comments on the protocol solicited by the UCLA Committee from four outside consultants (all of whom responded that more animal studies should be done prior to the proposed human experimentation), the UCLA Committee voted on July 16, 1980, to disapprove the protocol. Prior to the UCLA Committee disapproval, on July 10 and July 15, 1980, Dr. Cline inserted recombinant DNA into a patient in Israel and a patient in Italy. He had prior approval of the Israeli human subject protection committee to insert DNA, but not recombinant DNA, into the patient. The UCLA Human Subjects Policy Committee concluded that Dr. Cline's activities in Israel and Italy were not in conformance with requirements for UCLA scientists to have approval of the UCLA committee for their human subjects research even if conducted at a foreign site. The UCLA Institutional Biosafety Committee concluded that Dr. Cline's injection of recombinant DNA into humans was in violation of the NIH Guidelines for Recombinant DNA Research. Dr. Cline wrote on January 16, 1981, "I greatly regret my decision to proceed with the use of recombinant molecules without first obtaining permission from the appropriate committees. . . . I exercised poor judgment in failing to halt the study and seek appropriate approval. . . . I profoundly regret that I conducted these studies without adhering strictly to written guidelines."

While our NIH Committee was assemblying the facts in this case, UCLA also was investigating. The UCLA investigation was concluded with the acceptance of Dr. Cline's resignation as Chief of the Division of Hematology-Oncology of the Department of Medicine. Dr. Cline's letter of February 25, 1981, formally submitting his resignation as Division Chief stated, "My reasons for resigning relate to circumstances surrounding clinical trials of gene therapy conducted in Israel and in Italy in July of 1980. . . . I included recombinant DNA molecules in the preparations used to introduce new beta-globin genes into the patient's bone marrow without expressedly requesting to do so from the Israeli Recombinant DNA Committee."

Dr. Sherman Mellinkoff, Dean of the UCLA School of Medicine, in his reply on February 26, 1981, accepting Dr. Cline's resignation as Division Chief, wrote, "An entirely new and unprecedented experiment was knowlingly used in two patients without the approval of the appropriate UCLA and Israeli committees to conduct the experiments actually performed."

Dr. Cline's resignation as Division Chief included termination of other responsibilities associated with that position, including Director of the Medical Oncology Program of the Jonsson Comprehensive Cancer Center.](1)

Our Committee, recognizing the actions already taken by UCLA, made four additional recommendations, all of which were accepted by NIH Director Donald Fredrickson, and which now are in effect through May 1984.

Our first recommendation was "That, for each new research protocol involving human subjects with which Dr. Cline is associated, a written assurance of compliance, including certification of review and approval by a properly constituted Institutional Review Board, shall be forwarded to the NIH Office for Protection from Research Risks."

Our second recommendation was "That each project involving recombinant DNA molecules for which Dr. Cline is responsible . . . must be approved in advance by the Institutional Biosafety Committee and the NIH Office of Recombinant DNA Activities."

Our third recommendation was "That, for each current NIH award for which Dr. Cline is principal investigator, the Director of the awarding NIH Bureau, Institute or Division (BID) shall be supplied with a copy of this report and shall, after consultation with his National Advisory Council, recommended whether the NIH should continue the grant or contract, and if so, under what conditions." Dr. Fredrickson in accepting our Committee's recommendations wrote, "I . . . believe that the involvement of National Advisory Councils . . . in the actions recommended is an appropriate expression of the need for the scientific and academic communities and other sectors of the public to participate in administrative actions seeking to preserve the highest standards for scientific inquiry."

The review of Dr. Cline's active grants by the NIH National Advisory Councils occurred in September and October 1981. Even previous to the Council recommendations UCLA had requested that Dr. Cline be removed as program director on two NIH-funded National Research Service Awards (institutional training grants), and these requests were accepted by NIH.

At the autumn 1981 review of Dr. Cline's grants, the National Cancer Advisory Board recommended that Dr. Cline receive no further support from an extension until February 28, 1982 of a large Program Project entitled, "A Program in Medical Oncology." They recommended continuation of a research project grant to Dr. Cline entitled "Normal and Malignant Hematopoietic Cell Replication" until its previously scheduled termination date of May 31, 1982.

The National Arthritis, Diabetes, and Digestive and Kidney Diseases Advisory Council recommended continuation of Dr. Cline's grant "A New Method of Bone Marrow Culture" with certain additional reporting requirements.

The National Heart, Lung and Blood Advisory Council found Dr. Cline's actions "to be reprehensible and to warrant disciplinary action." They recommended termination of his NHLBI grant "Treatment of Hemoglobinopathies by Gene Insertion" at the end of the first year of support (i.e., on March 31, 1982). Dr. Cline appealed the NIH decision to terminate this grant, to the Department of Health and Human Services Grants Appeals Board. The Grants Appeals Board in a decision of August 30, 1982, upheld the NIH decision.

The fourth and final recommendation of our NIH Committee was "That, with each new, or competing renewal, application for NIH support subsequently submitted naming Dr. Cline as principal investigator, a copy of [our] report shall be supplied to the Initial Review Group to which the application is assigned, as well as to the Director and the National Advisory Council of the appropriate NIH BID. The report shall be considered in determining whether the NIH should fund the application, and if so, under what conditions." All grant applications from Dr. Cline reviewed subsequent to May 1981 have followed this procedure. This has included applications reviewed by The National Cancer Institute, The National Heart, Lung, and Blood Institute, and The National Institute of Child Health and Human Development. None of these grants has been funded.

This concludes my formal testimony. I will be pleased to answer questions.

Mr. **Gore**. Let me ask some questions before the day runs on too long.

Dr. Grobstein, I was quite taken with your formulation that we ought to concentrate on the short-term questions partly in the hope that success in dealing well with those questions will help us when we are confronted later on with these longer term questions, many of which will be more difficult than the short-term questions.

Is that a distorted summary of that point?

Dr. **Grobstein**. No; I think that is quite correct and it is the reason why I emphasize my feeling that whatever is set up should be of sufficiently long duration so that its memory, so to speak, can expand as it works.

Mr. **Gore**. Yes. I agree with that very strongly, and the kind of questions that you, Dr. Stich, sketched out for us, taking a much longer range view, whether or not you agree on the probabilities of any particular question arising, certainly they illustrate how difficult these questions are likely to be.

In fact, they are likely to be more difficult than any questions that humanity has ever had to cope with. I don't think that is an overstatement. It does strike me as very important that, because we are going to face those questions, to do the best job we possibly can with the shorter range questions, because not only will we hone our ability to make these judgments we will also set precedents that will influence the shape of the questions that will come later.

I think it is very, very important, therefore, that we make an extra effort above and beyond what might seem warranted by a given set of short-term questions so that the precedents are established well and that we get the practice we need in order to confront these more difficult questions later on.

It seems to me, Dr. King, that you focus on the extreme short term as a way to get started, the need for public debate. I certainly agree that is the initial question.

How do we further the public debate that is so necessary to a sensible resolution of these questions, and what kind of oversight and monitoring mechanism should be established and, as you say, Dr. Grobstein, what should the agenda be?

I think that a composite list made up of your recommendations, those of Dr. King and Dr. Alex Capron——

Ms. **King**. Mr. Chairman.

Mr. **Gore**. And let me just finish briefly.

Dr. Nightingale, among others, that a composite list of the characteristics which ought to adhere to this new governmental body I think would be extremely useful.

We are going to prepare such a composite list and include it in recommendations that we make.

Excuse me, Dr. King. Go ahead.

Ms. **King**. I wanted to add one statement that I don't believe anybody has mentioned before. It seems to me it makes a difference, a very minor point, about whether your commission members have a term for the life of the commission or whether you have a commission that has successive terms and people rotate on the commission.

The President's Commission on Ethics has a rotating membership. The RAC has a rotating membership. The National Commission for the Protection of Human Subjects did not.

It is my opinion that if you have a good commission to start with, that you work more effectively if you don't have rotating memberships.

Every time you bring in a new panel of commissioners, you lose substantial time in educating that new group of commissioners and also making them a part of the ongoing group and it is extraordinarily disruptive.

However, if you have a single group of commissioners, it may mean a limited life for a commission. So, there is a tradeoff, but I strongly urge that you have a set membership. It makes a big difference.

Mr. GORE. Well, I appreciate that recommendation.

You have discussed the relationships such a body ought to have to the established mechanisms, the institutional review boards and the others. I think that was a very helpful suggestion as well.

Dr. Stich?

Mr. STICH. Yes, if I may, could I add another word on the difference between long- and short-term focus?

Mr. GORE. Yes.

Mr. STICH. I don't know that I have any substantive difference with Dr. Grobstein, but it does seem to me that anybody should certainly not have an exclusive short-term focus; it seems to me that the best way to proceed is to keep long and middle and short term in view simultaneously, and that one can ask for decisions on short-term basis and discussion on longer term issues, and, as I understand it, that is what happened in the President's Commission.

Mr. GORE. I think that is true.

The metaphor that I like a lot is, someone said it would be impossible for a physiologist to understand the function of the human heart without reference to the larger organism within which it functions, and it would be impossible to adequately address the short-term questions arising in this field without reference to the larger context in which they arise, and it is partly for that reason why I think we need to make that extra effort to deal with the short-term questions now because we will better define the long-term questions that have to be asked and adequately answered.

Let me also say, Dr. Grobstein, I think your list is very impressive of the principles involved and all of the witnesses on this panel have given really excellent testimony and I appreciate it very much.

I would like to thank all of the witnesses that have appeared during all 3 days of these hearings. It has been a very, very instructive set of hearings and the subcommittee will continue to monitor the developments in this field and we will have recommendations to make as a result of this hearing to the full Science and Technology Committee, and it is my anticipation that in the next Congress, we will call for some action along the lines that so many witnesses have recommended.

I would like to thank the staff of the subcommittee and note for the record that Steve Owens and Jim Jensen have done what I think is a rather remarkable job in pulling all this together. Again, I would like to thank all of you.

You have helped us to put this set of hearings together and thank you for your contributions.

With that, the hearings will stand adjourned.

[Whereupon, at 2:20 p.m., the subcommittee was adjourned.]

APPENDIX

UNITED STATES HOUSE OF REPRESENTATIVES

COMMITTEE ON SCIENCE AND TECHNOLOGY

SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT

Hearings, November 17-18, 1982

Therapy for Genetic Disease: Ethics and Public Policy Issues

Statement of

Marc Lappé, Ph.D.*

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University of California School of Public Health

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* Supported by NEH/NSF Grant No. ISP-8114338

** The secretarial assistance of Ms. Alice Murata is gratefully acknowledged.

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The dramatic progress in devising therapies for previously untreatable diseases is to be welcomed as an advance that promises great alleviation of human suffering. But these same developments in genetic science also raise grave questions of how best to make the first experimental forays towards clinical application and to decide which therapies deserves our highest priority. These challenges bring us to a juncture where health imperatives, legal quandaries, and ethical dilemmas deserve our closest--and wisest--reflection.

It may be useful to recount how ethical questions have evolved over the last 10 years. The primary concern 10 years ago centered on the issues posed by compulsory genetic testing and screening. Among the disturbing prospects was the concern of some ethinic groups that mass genetic screening for the carrier state of serious disorders like sickle cell anemia could become the forerunners of a quasi-eugenic movement.

At that time I directed the Genetic Research Group at the Hastings Center, at Hastings-on-Hudson, New York, we had to decide whether it was more appropriate to talk about these problems or the ethical issues generated by genetic engineering. We opted for the former, in large part because we could not fathom that genetic engineering was as near on the horizon as it is so obviously now. Nor did we appreciate the subtleties of ethical analysis that would be needed for justifying the types of therapies now being considered.

In the recent past the issues of prenatal diagnosis and abortion concentrated on the questions of disclosure and consent. For whom should prenatal diagnosis be offered? Should it be only for those women over the age of 35 at risk for chromosome aneuplody, particularly Down's syndrome? Now we have to ask how, if and when should we move from offering an intervention that is essentially negative (selective abortion) to one where the same projected disease-state is considered for treatment. It is precisely at this juncture that the first major ethical questions of gene therapy are raised.

1. Ethical Issues in Therapy of Genetic Disease

Metabolic disorders (e.g., Niemann-Pick disease) or, indeed, some of the X-linked disorders (e.g., Lesch-Nyhan disease) have only recently become subject to diagnosis in the intra-uterine environment. They may now be subject to therapeutic intervention. We also have reasonable prospects for therapy of severe combined immune deficiency. These prospects pose major ethical questions in clinical judgment and patient rights.

When do you disclose to an expectant mother that you have an experimental therapy on the near horizon? Initially, you may have techniques that have only proven efficacious in animal models, or in the first human cases. According to some researchers, where intra-uterine diagnosis has confirmed the presence of a fetus with that now potentially treatable disease, it will be difficult in all but a few cases to offer the uncertain option of an experimental therapy, when the certainty of diagnosis and abortion promise a clearer and simpler solution to the problem. Williamson [1] has observed that "the correction of a disease by gene therapy will be worthwhile only if there is no other, simpler and more effective technique available". Yet, ethicists might argue that the presence of even a potential therapy diminishes the acceptability of late abortion.

Clearly, this is a circumstance calling for the most heightened ethical sensitivity. It is entirely likely that parents who have had an affected child are less than ideally situated to give a free and voluntary consent to the therapeutic procedure.

Many of the conundrums posed by gene therapy resolve to a basic dilemma: How can parents be helped to determine when measures that may or may not promise benefits outweigh their choice of a selective abortion? Is it ethically acccept-able to opt for selective abortion to avoid the prospect of an infant's facing a life fraught with suffering when potential therapies have reduced that likelihood substantially? When do the uncertainties regarding the lifelong value of an intervention reach the point of sufficient assurance to warrant routine offering of the therapy?

Characteristically, ethicists do not have many more answers to this type of problem than do physicians or parents, but they sometimes help in framing the balancing considerations these kinds of questions need to be resolved. Just acknowledging that there will be dilemmas of this magnitude for a substantial number of genetic diseases that will be in line for experimental therapies is important in itself (cf [1]).

Perhaps the greatest ethical dilemma is posed by the very grave and irreversible character of the clinical course of most genetic diseases. The belief is widespread that extreme suffering calls for extreme interventions and equally extreme therapeutic modalities. For many disciplines, particularly oncology, it has become a traditional precept to use those individuals with the most advanced incurable, and irreversible disease as the first subjects for therapeutic intervention. Consider the therapies that have been proposed for individuals with leukemia or other forms of incurable cancer, for instance, radical neck dissection and radiation therapy for head and neck tumors. In these instances, the most extreme therapeutic interventions are reserved for individuals nearing the terminus of a disease process.

Ironically, clinicians now recognize that some of these experimental modalities are most effective or, sometimes, only effective when introduced earliest in the disease. Such cases undercut the rationale for using terminal patients as the subjects for novel interventions. The message to genetic therapists is clear: Do not wait until a child has the full ravages of a heritable disorder before instituting therapy.

This, however, raises the joint questions of proxy consent and the readiness of a particular technologic intervention for treating a disease. Formal guidelines for the orderly and ethically acceptable generation of genetic therapies based on recombinant DNA techniques do not yet exist except by reference to existing HHS and NIH guidelines for experimentation [2]. While these guidelines identify the importance of having appropriately defined techniques with reasonable prospects for therapy based on animal or primate models, the first attempts at human gene therapy have been done without having suitable models or proven animal test systems [3,4].

Ethical and sound medical precepts dictate that genetic therapies be preceded by adequate pre-human testing. Once requirements of efficacy have been satisfied, the safety of these techniques must also be proven--a process hampered by the dearth of animal models for important human disease. The possibility of iatrogenic illness must be balanced against the consequence of the illness that ensues from failure to intervene. Thus, there must be some procedure and process for delineating the relative risks of intervening vs the consequences of not intervening, even when benefits cannot be completely detailed.

2. Issues of Public Support

Given the extrapordinary progress in this field, it is not too early to begin to consider the question of how we should best move genetic therapies into the mainstream of clinical medicine (cf [5]. In the very near future genetic therapy for diseases like Lesch-Nyhan or sphingolipidoses will attain widespread public importance. Previously therapy-resistant disease such as childhood-onset diabetes may call for treatment modalities that include genetic and non-genetic interventions (e.g., vaccination programs). Which approaches require wholesale public support through federal funding or new insurance programs? How can treatments be used on the scale necessary to achieve genuine public health objectives? Some, but not all programs, may pass the test of a positive benefit to cost ratio. Others may be justified on more humanitarian grounds. Which therapeutic advances deserve the highest funding priorities?

Questions of resource allocation are as critical now as are the issues raised by experimentation directed at the individual patient, and it is here that traditional ethical norms begin to fray at the edges. Weighing public and individual good is a delicate exercise at best. One test of whether it is appropriate to allocate public resources for an intervention has relied on measurements of the public consequences of disease entities, usually by some crude measurement of the cost/benefit ratio (e.g., the costs of intervention times the frequency of the occurrence of a particular disease and its cost were it to be left untreated). A significant portion of genetic diseases are by their very nature exquisitely rare disorders; thus, if one uses a measurement of human suffering multiplied by the relative frequency of any individual genetic disease, the "burden" of that disease would provide a poor basis to justify investment of public funds in developing modalities of treatment. However, all major Mendelian recessive genetic disorders together comprise a significant burden of disease, particularly in childhood where they account for a large portion of pediatric hospitalizations (up to 30-40 percent) and affect considerable numbers of individuals (estimates are as high as 1 percent [1]). Hence, as I will argue below, it may be important to encourage research strategies that may lead to universalizable models, over those earmarked for single, rare genetic disorders.

3. Distinguishing Values Basic from Those of Applied Research

A fundamental problem in identifying techniques with universalizability is that they rarely can be separated from less valuable approaches when they are at an experimental stage. Sometimes, early experimental approaches that appear promising as general treatment modalities are rushed into application, with deleterious effects on basic research [6]. When clearly experimental techniques are prematurely applied to treatment modalities as occurred in the work of Martin Cline, [3,6], a gap opens between scientific credibility and public support.

Public agencies have also reinforced a view which identifies single diseases as appropriate funding targets rather than whole classes of diseases. We have seen incommensurate decisions made in garnering statewide support for a few rare genetic diseases (e.g., a special program for Huntington's disease in California) or for some that are not so rare. The more common coagulation disorders (e.g., hemophilia), which are amenable to treatment, have repeatedly been proposed for support in the State and federal law-making bodies. As a counterpoise to this trend, some legislators can now point to the fiscal debacle that ensued when renal transplantation and support for end stage renal disease was given total federal support. Let us hope we do not perpetuate this "disease-of-the-year" dilemma for hereditary disorders. I suggest that part of the solution is to encourage funding priorities that encourage the development of those techniques that have the greatest prospect of generalizability. To do so means establishing effective treatment models for whole classes of molecular or biochemical disorders.

4. Specific Treatment Modalities

How close are we to developing therapies with this kind of general applicability? Indicators of early prospects for successful models suggest that that problem of assigning priorities should be grappled with right now. The following discussion indicates research avenues that bring us to developing therapies that might lead to a more general solution for genetic diseases.

The five genetic interventions in Figure 1 demonstrate the feasibility of inserting specified gene sequences into rapidly developing embryos such that there is a reasonable prospect that these gene sequences will become encoded in the somatic cells and, in one case, in the germinal epithelium and germinal tissues of the resulting organism. While human embryo therapy has ethical problems of its own (cf [1]), success in this area is a harbinger of greater likelihood of effective treatments than regular insertion of functional genes into living tissues.

The first study, demonstrating the technical feasibility of inserting a gene for human insulin into fertilized mouse eggs and obtaining postzygotic expression of this gene, was done by Kurt Burke at the University of Geneva in

FIGURE 1. REPORTED GENE TRANSPLANTATION ATTEMPTS

Human insulin gene transplanted into fertilized mouse egg cells.	Collaboration between scientists in Switzerland and California.	The transplanted gene persisted through embryonic development.
Human interferon gene transplanted into fertilized mouse egg cells.	Yale University.	The gene persisted into the next generation of mice.
Virus genes for thymidine+kinase transplanted into fertilized mouse egg cells.	The Institute for Cancer Research, Fox Chase, PA.	Thymidine+kinase was produced by the mouse embryo cells.
Two people given blood-forming cells containing a gene for a component of hemoglobin.	Scientists at U.C.L.A. in collaboration with doctors in Italy and Israel.	No conclusive result reported; a scientist reprimanded by the National Institutes of Health.
Two infants infected with a virus to treat an enzyme deficiency.	Scientists at Oak Ridge National Laboratory Collaborating with doctors in West Germany.	Treatment failed to prevent mental retardation by providing enzyme to the infants.

Redrawn from The New York Times, September 8, 1981.

Switzerland and, coincidentally, by Axel Ullrich of Genentech Inc. (See review by Ullrich [7]). A related experiment, by Frank Ruddle at Yale, was even more dramatic in that the interferon gene was transplanted into fertilized mouse eggs; subsequently, he and his co-workers demonstrated incorporation of this gene into the germinal epithelium and the transfer of the gene into a second generation (cf Gordon et al., [8]).

In the third study a well-characterized viral gene, the gene for thymidine kinase, was transplanted into a fertilized mouse egg by Beatrice Mintz of the (Institute for Cancer Research, Fox Chase. Dr. Mintz and her co-workers demonstrated the expression of viral genes in a murine test species, thereby opening the prospect of gene therapy by overcoming of the major obstacle of ensuring expression of heterologous genetic material. Her work also affords an avenue towards resolving the problem of how to get enought cells transfected to develop a sufficiently numuerous population of transformed cells to make the necessary gene product. Apparently, you can be quite successful if you can start this process early enough (cf Pellicer et al., [9]).

The next study involves the principle used by Dr. Mintz--namely, trying to get a clonal population of cells in this case, bone marrow cells to pick up a specified gene sequence, and looking for evidence of expression. Martin Cline at U.C.L.A. attempted to use bone marrow treated with cloned DNA sequences to repopulate the leg bones of two young girls, (in Italy and Israel). His work was apparently both unsuccessful and ethically questionable (cf [3,6]).

The last example was the use of the Shope papilloma virus, to infect two arginase-deficient infants so that they would thereby, regain the ability to produce arginase. Neither child showed clinical improvement attributable to the virus treatment, perhaps because sub-infective doses were used (see Rogers [4], for a full discussion and defense of this protocol).

5. Ethical Issues

These examples, as heady and exciting as they are for the prospects of therapy, raise major ethical questions. According to some ethicists, such as Paul Ramsey of Princeton [10], the inviolability and presumed right to normal existence of a person have unfortunately been taken to imply an obligation to intervene. Thus, if one can specifically identify at an embryonic or even zygotic stage an affected individual for whom one has a possible gene therapy, one may be morally obligated to try to "rescue" that individual. Yet, we as a society now condone abortion through the fifth month of gestation for any hereditary or chromosomal disorder.

Research on fetuses also overlooks the problem of absent consent, possible harms outweighing benefits, and the knotty, unresolved question of our obligation to treat at any cost. Moreover, treating persons in advance of successful animal experimentation denies those individuals respect by making them experimental subjects to unproven techniques for the sake of experimentation alone.

6. Issues of Social Justice and Strategic Considerations

We have seen that the optimism we may bring to advancing these therapeutic models is tempered by at least three broad sets of problems. The first is that there is no agreed upon norms or guidelines for setting priorities in genetic research. Some may argue that this is exactly the right moment to have an open-door policy for encouraging the broadest possible avenue of therapeutic experimental ventures. Others would point out the importance of moving cautiously with regard to "rescuing" those individuals who have fatal, incurable diseases because of attendant excesses.

A second major problem, which we may encounter in the next five years, is how to allocate resources to treat genetic diseases. The third problem, is how to decide, after an array of alternative therapeutic modalities has been developed, which one is the most appropriate for treating groups of related genetic diseases.

All of these issues are still in embryonic stages. Each turns on the question of how to define the readiness of a technique to be moved first into an experimental arena and then into an applied public health arena, where it becomes an acceptable modality for treatment.

But underlying all of these problems, is a fourth and perhaps more critical dilemma: how do we assure that social justice will be reinforced and not undermined as these techniquesproliferate. I have already shown that where new modalities of prenatal medical technology have become available, they are used first and most extensively by upper socioeconomic groups [11]. A new case in point may be juvenile onset diabetes. Although most researchers recognize the complex etiology of diabetes--e.g., its apparent dependence on certain HLA phenotypes and the possible rule of viral infection and autoimmune phenomena in generating the disease (cf [12])--until recently few have proposed interventions to prevent its pathogenesis (cf [13,14]). Instead, clinicians have relied on the apparent success of treating the pathological manifestation of the disease with insulin. Some would argue that insulin therapy had led to a "hyperfocus" on chemotherapeutic intervention in preference to other treatment modalities. Other interventions, such as the use of immunosuppresive agents to dampen the immunemediated damage to the islets of Langerhans [13] or immunotherapy to prevent type I diabetes[14], are just now being attempted. All such new modalities must now compete for funding with recombinant DNA technologies which have been developed for making pure human insulin.

It would be naive not to recognize that substantial investments in the last three years have gone into developing efficient ways to synthesize pure human insulin. At the same time, proportionately fewer dollars have been allocated to fewer scientists for basic research that could define the actual structure of the insulin gene and its relationship to other genes (cf [15, 16]). In principle, it is this latter approach which is the more valuable, because it can lead to prevention rather than palliation strategies.

From a public health viewpoint, investigating the control and function of the insulin gene may be more likely to give long-term benefits than the application of insulin as a chemotherapeutic, after-the-fact treatment. Yet, our present investments are heavily skewed in favor of reaping immediate financial rewards, instead of being directed toward preventive strategies with possibly greater long-term health benefits. The likelihood that significant funding would go to this latter course of intervention is substantially diminished by the fact that most of the dollars for research in the area of insulin production and treatment of diabetes are concentrated in the private sector, and out of public sector control.

This trend, should it continue, has two very negative consequences: First, the normal modalities of allowing scientific feasibility and heuristic appeal of experimental approaches to guide the direction of research would be displaced by the financial incentives to develop therapies that could be quickly monetized. This kind of displacement could mean that the initial stages of development of long-term solutions to complex polygenic diseases like diabetes and hypertension may not be evolving in the most efficient, least costly, or scientifically most desirable directions.

A related problem, the development of single-gene products that are attractive to private sector investors, is likely to be contingent on the existence of a very large population of affected individuals in economic need of this therapy. Development of such a posture by industry would ignore the possibility that the therapeutic modalities that work best and have the greatest potential for generalization to other disorders may well be model systems developed for treating very rare human genetic diseases. For instance, an approach for treating hypoxanthine-guanidine phosphoribosyltransferase deficiency in Lesch-Nyhan disease from cloned gene segments that code for HGPRT could very well provide a model for treating a large spectrum of otherwise rare inherited disorders (see [17] for a review of this problem). But no corporation in its right economic mind would invest heavily in developing a specific therapy for that rare an entity. The notion that therapies directed at more prevalent diseases are more justified than those directed at rare ones should not be an ethical norm for basic research. It may be important to distinguish among those therapies are going to provide the most useful models for generalizable interventions and which ones are going to be left at way stations, albeit effective ones, for treating rare genetic diseases. But, in the absence of reliable techniques for distinguishing which approaches have the possibility of extension to near-related diseases, it is foolish, and perhaps even unethical to allow short-term gains to direct research priorities.

One promising approach has centered on interventions involving transplantation of clonally proliferating cells which can potentially restore the deficiencies or defective gene products that ensue from a broad constellation of disorders. Both inborn errors of metabolism, α_1-antitrypsin deficiency combined immune deficiency states, are now being successfully treated by bone marrow or fetal liver transplantation (cf[18]). These procedures provide the basic research paradigms both for understanding the more widespread problem of deficiency states and for studying more closely heterozygous individuals who have more moderate clinical problems.

7. Private Public Sector Funding

These triumphs of therapeutic invention may become less rather than more common as the result of a wholesale shift of technologies that would otherwise be supported by the public into the private sector. Where economic incentives become mixed with scientific ones, basic research can get skewed into applied research by "priority" schedules and policy decisions that come to be made by Boards of Directors rather than scientific panels. As a result of the present funding climate for genetic research, the very techniques that offer so much promise for understanding basic science, are being jeopardized. "Cost-effective" programs designed to generate profits will almost always be those which generate hard commodities, e.g., drugs that alleviatesymptoms of disease states, rather than the soft commodity of knowledge.

This situation leads to a possible premature collapsing of basic science into applied science. Scientists would do well to maintain the distinction between those elements of their work which are basic research and those that are projected for early application. It may also be critically important for funding agencies to foster and promote basic research. Retaining a modicum of recombinant DNA research e.g., for plumbing the structure of the human genome, may be more important in the long run than are technologically elegant techniques for inserting economically or medically desirable gene sequences.

8. Possible Solutions

As a first step, it makes good ethical and scientific sense to have competing approaches for treating genetic disease, some of which focus on basic scientific strategems and others that are designed to promote development of specific new therapies. Second, it is important to acknowledge that competition between alternative modalities of treatment or diagnosis is to be encouraged rather than quelled through monopoly control of gene products as may now be happening with human insulin. Third, the value of doing basic research should not be obscured by economic incentives to develop a technique for the sole-purpose of reaping early rewards or short-term gains: such techniques may not provide the most long-lasting contributions to scientific knowledge or health. For example, it may be much more attractive to develop approaches and techniques that lead to the recolonization of a genetically deficient individual, through marrow, liver, or kidney transplants, than to design specifically engineered gene-product therapy. Unfortunately, the economic imperatives of the marketplace have led to the proliferation of micropackaging industries that purport to develop lyposome or other membrane packages for delivering enzymes or other structural genes to individuals who lack them, long before there is any real evidence that such approaches.

Although I am criticizing private public sector approaches, I do not purport to know which group necessarily has the "right" approach to a given genetic problem. But I can conclude that financial incentives serve as a constant skewing device that may set priorities with regard to financial imperatives rather than medical and scientific readiness. It is this last point that I would hold up for review: is it in our best interests to have interventions increasingly in the hands of those whose incentives for developing them is often tempered by issues of both medical efficacy and financial return, as compared with those in the public sector who receive funds from the public weal. Only the latter group is likely to consistently base its research on science's internal guide rules and to be relatively value-neutral. Yet, science is freely conducted when scientists begin by looking for the most useful scientific approaches to solving a problem and only secondarily, with having public policy makers, either federal or state, decide which modalities provide the greatest public benefit.

The disparity between private and public sector research also leads to a critical tension between the selection and choice of patients of individualized therapy in contrast to considering therapies that can be generated for *communities* of patients with like diseases. The absence of formal acknowledgment (circa 1981) of this problem underscores the fact that discussion of distributive justice, scientific freedom and public vs. individual good has not yet taken place at a national level. As we begin to disband the budget of the specific National Institutes directed at looking at genetic diseases, arthritic diseases, or diseases of circulatory systems, in favor of allowing *laissezfaire* economics to move research priorities, we are left with a real quandary. How much scientific freedom and creativity do you lose when you abandon a federal base of support for disease entities? The full impact may also depend on the degree to which we sacrifice public accountability and public control for regulating how tecynologies are allocated to the medical sector.

8. Recommendations

That then leaves a major ethical problem in moving towards genetic therapies. It would be desirable to consider having a public agency, perhaps as a subdivision within the National Institute of Health's Genetics Disease Branch charged with the funding and oversight of genetic therapies. It may be necessary to maintain rules and procedures (e.g., patentability or marketing of proprietary drugs) that allow the private sector to reap benefits. But if we do, the public has a right to request that the benefits that are going to be reaped, both medically and economically (for instance, in the synthesis of insulin), be returned proportionately to them, rather than to the stockholders of the corporations involved. Thus, while it was public monies that supported the research which led to the basic patents awarded to Stanford and the University of California at San Francisco, the companies who make the recombinant DNA precursors and products based on these patents return only a pittance ($10,000) to the schools, and still less to the public at large to whom they are able to charge whatever the market will bear.

Issues of social justice are raised when genetic therapies become wholesale commodities to be sold in the marketplace, rather than being used as models for therapies for broad ranges of diseases. Although they have now gone into the private sector, the origins of some of these techniques were in the public sector. In allocating these exquisitely effective and elegant modalities, it will become important to recognize that the issue of justice and fairness demands greater equity and profit-sharing in their distribution.

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